The Treatment of Menorrhagia with an Evaluation of Endometrial Ablation and its Evolution.

STUART ANGUS JACK

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GLOSSARY

ALA – Aminolevulinic Acid

AM - Adrenomedullin

AVM – Arterio-venous malformation

DUB – Dysfunctional Uterine Bleeding

EA- Endometrial Ablation

ELA – Endometrial Laser Ablation

ELITT – Endometrial Laser Interstitial Thermotherapy

FEAT – First Generation Endometrial Ablative Technology

GNRHa – Gonadotrophin Releasing Hormone analogues

HADS – Hospital Anxiety and Depression Score

HNPCC – Hereditary Non Polyposis Colonic Carcinoma

LAVH – Laparoscopically Assisted Vaginal Hysterectomy

LNG – IUS – Levonorgestrel Intrauterine System

MBL – Measured Blood Loss

MEA – Microwave Endometrial Ablation

MMP – Matrix Metalloproteases

MRI –Magnetic Resonance Imaging

NO - Nitric Oxide

NHS – National Health Service

PBLAC – Pictorial Bleeding Assessment Chart

PGF2α – Prostaglandin F 2 Alpha

QOL – Quality of Life

QUALY – Quality Adjusted Life Years

RCOG – Royal College of Obstetricians and Gynaecologists

RCR – Royal College of Radiologists

REA – Rollerball Endometrial Ablation

RCT- Randomised Controlled Trial

SEAT – Second Generation Endometrial Ablative Technology

SPRM – Selective Progestrone Receptor Modulators

TBEA – Thermal Balloon Endometrial Ablation

TCRE- Trans Cervical Resection of the Endometrium

TAH – Total Abdominal Hysterectomy

TV USS – Trans-vaginal Ultrasound Scan

UFAE – Uterine Fibroid Arterial Embolisation

VEGF – Vascular Endothelial Growth Factor

VH – Vaginal Hysterectomy

Definitions used in this thesis

1. Dysfunctional Uterine Bleeding – Abnormal uterine blood loss either regular or irregular, occurring from a uterus of up to a ten weeks sized pregnancy on clinical examination with a normal endometrial pathology
2. Menorrhagia – heavy menstrual bleeding, regular or irregular greater than 80 mls per cycle.

Declaration

I hereby declare that I personally conducted the work described in this thesis, collected and analysed the data and composed its presentation. My external supervisor was Dr Sharon Cameron and direct clinical supervision and methodological support was provided by Dr Kevin G Cooper. Dr Cooper has assisted in the operative procedures in the randomised control trial of microwave endometrial ablation in a postmenstrual phase and in the randomised control trial of microwave endometrial ablation versus rollerball endometrial ablation. The trial comparing microwave endometrial ablation and rollerball ablation was conducted as part of a research project funded by Microsulis PLC.

All quotations have been distinguished by quotation marks and references have been identified by superscript numerals and are referenced in full in the bibliography. This work is original and has not been submitted in any other application for a degree.

The trials of microwave endometrial ablation were completed between August 2001 and November 2002 whilst the author was a Chief Scientist Office Research fellow in the Gynaecology Unit of Aberdeen Royal Infirmary. The 5 year follow-up of the randomised control trial of medical treatment versus transcervical resection of the endometrium was performed between August 1999 and August 2000 whilst the author was a Registrar in Obstetrics and Gynaecology in Aberdeen Royal Infirmary.

The opinions expressed are those of the author.

Stuart Jack
May 2006

Aims

Referrals to gynaecology from primary care of women with excessive uterine bleeding are common, with up to 30% of women reporting their menses as abnormal.
It is a condition which has a significant adverse effect on quality of life. The cost to the Health Service is significant. In the United Kingdom 57,000 hysterectomies alone are performed per annum for menorrhagia. The 7 million pounds spent per annum in the UK on prescriptions for medical treatments is similar to the amount expended on surgery. A majority of hysterectomies performed will be for dysfunctional uterine bleeding, on anatomically normal uteri, uteri that are eminently suitable to ablation. Despite advances in medical treatment, hysterectomy remains an effective procedure, releasing women from the burden of excessive menses, but at a cost. The operation is successful, with the highest recorded levels of satisfaction of any treatment option. The financial implications are not insignificant with a cost to the health service and a physical cost to the patient. Up to 1 in 30 will have a significant complication. Furthermore patients take 6 - 12 weeks to fully recover. New modes of hysterectomy – laparoscopic assisted vaginal hysterectomy, total laparoscopic hysterectomy and laparoscopic supra-cervical hysterectomy promised shorter hospital stays but have associated increased technical demands on the surgeon, possibly increased complications and would certainly not appear to be a technique that all could master.

Medical treatments can be effective but prescribing can be misguided with ineffective regimes deployed in a vacuum of evidence.

Endometrial Ablation, a conservative alternative to hysterectomy offers comparable but lower levels of satisfaction. Endometrial ablation is established as an alternative surgical

treatment to hysterectomy. The procedures offer rapid treatment, short hospital stays and quick recovery at a lower economic cost than hysterectomy. Traditionally Endometrial Ablation has been offered once a trial of medical treatment has failed although there is good evidence to show that ablation should be offered to eligible patients early.

The trials reported in this thesis aim to explore the evidence base for the treatment of excessive menstrual loss, and establish a hierarchy of treatment for excessive menstrual bleeding from medical treatment, through first generation ablative techniques and ending with second generation ablative techniques. The traditional rational of ablation only being offered after a failed trial of medical treatment is explored. The possibility of moving endometrial ablation, a traditionally theatre based treatment into an outpatient setting is explored. The incidence of individual surgical procedures for menorrhagia is explored comparing recently published figure for England and Wales with Scottish national and regional Grampian Figures. Finally the evidence base is concluded and summarised with suggestions for future research.

Abstract

This thesis is based on work performed in the Department of Gynaecology of Aberdeen Royal Infirmary. This is a regional referral centre with an established reputation in menstrual research, focusing on surgical trials. The work of this thesis continues and expands on this.

Chapter 1 outlines and reviews the current literature on the treatment of menstrual disorders. The aetiology, epidemiology and options both surgical and medical are reviewed. A detailed review of the development, scientific and technical aspects of Microwave Endometrial Ablation is made. The evidence base is reviewed and discussed with a focus on randomised trials.

Chapter 2 describes the 5 year follow up of an original trial comparing women initially referred to a gynaecologist with excessive menses who were randomised to either standard medical treatment or endometrial ablation in the form of Transcervical Resection of the Endometrium (TCRE). This represents the longest follow up of women randomised to medical treatment for menorrhagia. Those allocated to ablation were significantly more likely to report themselves as totally satisfied at 5 years as those allocated medical treatment. Acceptability was high for both arms but only 20% of women treated medically would recommend this to a friend compared to 79% of the ablation arm. Amenorrhoea rates were significantly higher in the ablation arm versus the medical arm (88% versus 66%). Quality of life measures using the generic tool SF 36 revealed that scores for the women in the ablation arm were restored to normative levels in all 8 subsets, whilst this was improved in only 4 for the medical arm. During the follow up period 77% of those in the medical arm underwent ablative surgery. The impact of offering ablative surgery early did not result in an increase in the incidence of recourse to hysterectomy with similar numbers in each arm (17% versus 18%) being hysterectomised at 5 years.

Chapter 3 describes a multi-centre international randomised controlled trial comparing the first generation technique of Rollerball Endometrial Ablation (RBEA) with the second generation technique of Microwave Endometrial Ablation (MEA). This trial had 8 centres, both academic and private, in the United States, Canada and the United Kingdom. The trial randomised 322 women to MEA or RBEA in a 2:1 ratio. Menstrual Loss (PBLAC) diaries were used in the recruitment, follow up and definition of success (PBLAC score < 75). When comparing women allocated to MEA versus those allocated to RBEA they reported similar success rates and satisfaction. Higher post operative amenorrhoea rates were reported in the MEA arm but the result was not significant. In the subgroup of women with BMI's of over 30kg/m^2 MEA was significantly more likely to be associated with success. The presence or absence of non-obstructing fibroids (< 3cm) did not affect success rates or amenorrhoea rates between MEA and RBEA. MEA

treatment was significantly more often performed under local anaesthesia. This trial established MEA as being comparable in the majority of outcome measures to RBEA.

Chapter 4 describes a randomised controlled trial of MEA performed in an outpatient setting in the early post menstrual phase to standard treatment performed in a day case theatre after endometrial preparation. All procedures were performed under local anaesthesia plus or minus sedation. 210 women were randomised in a 1:1 ratio to the treatment arms. Significantly more women found treatment post menses acceptable (89.5% versus 76%). Similar numbers were totally or generally satisfied (92.5% versus 84%). Amenorrhoea rates were similar (55.9% versus 61.9%). A significant difference in direct cost was seen with treatment as an outpatient in the post menses arm costing £124 less than treatment in day case theatre after endometrial preparation.

Chapter 5 reviews the rates of surgery for excessive menstrual bleeding in Scotland and the Grampian region from 1998 – 2004. A 43% reduction in the hysterectomy rate is seen in Scotland over the time scale. A smaller reduction (34%) is seen in the figure for Grampian. This may be a reflection of Aberdeens pro-ablation stance and early general uptake of the procedure .A 25% reduction is seen in the total number of procedures in Scotland. The ratios of hysterectomy to ablation alter over time with a reduction from 5:1 to 1.7:1 seen. The ratio is Aberdeen is more marked with a ratio of 0.5 to 1, twice as many ablations being done as hysterectomy. The low uptake of vaginal hysterectomy and decline in minimally invasive technologies of Laparoscopic Assisted Vaginal Hysterectomy are outlined. Overall an increase of 65% in ablation rates in Scotland is seen with a shift from first generation to second generation techniques (11% reduction in 1st versus a 65% increase in 2nd generation technologies).

Chapter 6 reviews the conclusions made form the work described in this thesis and there relevance to medical practice. Suggestions are made for areas of future research.

Chapter 1 Literature Review

1.1 Heavy menstrual loss – aetiology, epidemiology and options for management.

1.1.1 Introduction

Menstrual bleeding is a natural biological event caused by the shedding of the functional layer of the endometrium in response to the withdrawal of progesterone in the absence of a conception. Despite this event being a biological process, familiar to over half the population, it is surrounded in mystique and seldom openly talked about.

Cultural attitudes vary enormously with the majority featuring on an unclean and impure attitude towards women whilst they are menstruating.[1] This does nothing to encourage any openness or understanding of menstruation in society. The prejudices of a historically male dominated society may be reflected in these attitudes. Many religions ban menstruating women from Holy places or participation in prayer whilst menstruating.[1] Not all cultures however take such a negative attitude towards the onset of menstruation. In Australia certain Aboriginal tribes' people celebrate the onset of the menarche as a sign of reproductive maturity and a rite of passage into the adult world. [1]

Modern women will have many more menstrual periods than their ancestors. The combination of lactation and gestation induced amenorrhoea resulted in Victorian women probably only having 40 periods in a life time, whilst prehistoric women would have had only a handful of menses.[2] In contrast the modern woman with small family size and a limited time spent breast feeding can expect to menstruate on average 400 times during her life time.[2] Women's attitudes towards menstruation would appear to

change with time and present day attitudes may have created a new concept of 'Menstrual Intolerance'. Modern women have an expanded role in society; they are mothers, partners, home economists, and careerists. The addition of menstruation with its attendant symptoms to their multifactorial roles is seen by many as unnecessary and undesirable, especially once their reproductive aspirations have been met.

1.1.2 Epidemiology

Menorrhagia is commonly defined as the loss of greater than 80 mls per cycle a definition derived from the 90th percentile from the mean of 40 mls per cycle in a Swedish population study [3]. The 80 mls definition of menorrhagia has been validated for a UK population. [4] Many would argue against the clinical relevance of this statistically derived value. In reality a significant number of women on a Western diet will become anaemic when losses exceed the 50 – 60 mls mark. [3]

The 80 mls definition has been explored in a Scottish Population. Two sister papers published simultaneously by the same group looked at this definition. They assessed firstly the clinical factors that would predict a menorrhagic blood loss [5] (using the greater than 80 mls measured blood loss definition) and secondly they looked at the clinical usefulness of the 80 mls definition [6].

They surveyed just under a thousand women (n= 952) with a menstrual complaint recruited from 3 clinics from Edinburgh and Glasgow [5]. Of the subset of women complaining of subjectively heavy periods (n= 865) they assessed the measured blood loss on standardised sanitary wear as per Hallberg and Nilsson for 226 women collectors (26%). Only 34% of those with subjective heavy loss fitted the definition. They reported that the clinical features that were more strongly associated with menorrhagia were the rate of change of sanitary wear, the total number of products used, the need to change protection in the night, the size of clots (> 50 pence piece) and poor iron status. They suggested that a model based on these features predict reasonably well the presence of genuine menorrhagia blood losses. They reported strong associations with the subjective reporting of very heavy period and excessive loss when compared to the

remainder of the women, which goes against the general clinical perception that women are poor judges of their loss.

The sister paper published by the group looked at the usefulness of the 80 mls definition of menorrhagia [6]. In the paper the women reported a range of problems with their periods, but absolute volume (31.2%) was less prevalent than period pain (37.5%), mood change (35.7%), and change in the amount (volume) of the period (33.8%). Although there were associations with volume, these associations were due to the heaviest and lightest of the loss groups, whereas the 2 groups with loss either side of 80 ml were virtually indistinguishable. They concluded that the 80 ml criterion for menorrhagia is of limited clinical usefulness because it is prognostic neither for problems nor iron status and apparently does not guide management.

As a cause of iron deficiency anaemia when looking at the world- wide perspective, menorrhagia is a trivial cause compared to the chronic anaemia of parasitic disease burden. It is, however, the number one cause of anaemia in the developed world. [7] Haematological indices in the vast majority of women complaining of menorrhagia will reveal a normal haemoglobin. Only 15 – 29% will display anaemia, with many more displaying a depletion of iron stores as revealed by a low serum Ferritin. [3;4]

The concept of tightly regulated regular menstrual losses with an entirely predictable almost regimented pattern is a falsehood. Enormous variation between individuals and over time within individuals is observed. A United Kingdom epidemiological survey of women's menstrual loss in the community revealed how common menstrual symptoms are. They used cumulative incidence rates over a twelve month period and revealed 25% reporting menorrhagia, 21% reporting heavier periods, 29% reporting changes in their cycle, 21% reporting a short cycle , 15% reporting a long cycle , 17% reporting inter-menstrual bleeding, 6% reporting post coital bleeding and 9% reporting prolonged periods. [8] For a woman the greatest cycle regularity is seen in the mid 20's, with the greatest irregularity seen at the extremes of reproductive life – the peri-menarche and peri-menopause. [9;10] The majority (90%) of ovulating women range between two and

nine days most commonly four to five days. Ninety percent will lose the majority of their loss during the first 3 days with days 1-2 being the heaviest. [9;11]

When analysing data from different studies it is interesting to note that a fairly constant figure of around 30% of women report their menses to be excessive and often interfering with their lives. [12;13] This is in dispute with the figures from population studies by Hallberg[14] and Cole [4] where you would expect 10% of patients to be suffering from excessive menstruation (> 80 mls/ cycle).

Menorrhagia or excessive menstrual loss has associated health implications. As a condition it is very rarely life threatening, rather it affects patients' working and family life and is associated with a measurable reduction in quality of life.[15] The economic costs to women in terms of costs for sanitary protection and to the country in days lost to work represent an often unseen and unmeasured cost.

The subjective nature of the complaint of menorrhagia or excessive menstrual bleeding is seen in the work by Hallberg et al.[14] 40% of women with objectively heavy periods (> 80 mls per cycle) thought their periods to be moderate or light and 26% of those with losses(< 60 mls per cycle) felt their periods to be excessive.

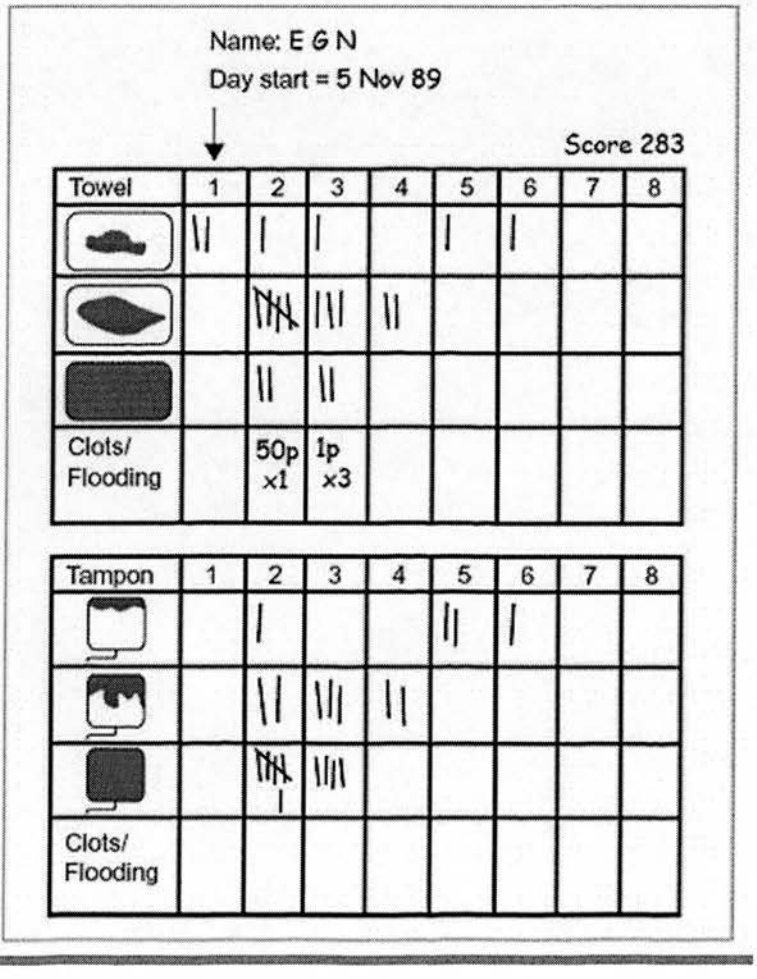
Clinical markers taken in a history such as length of cycle or number of pads used have limited reliability. Cycle length has been compared to menstrual blood loss in a study by Rybo. [16] The study revealed only 45% of women who bleed for more than 7 days having objective menorrhagia, with 78% of the menstrual loss occurring in the first two days and 91% by day three. The frequency of sanitary wear changes is highly influenced by the patient's personal hygiene habits.[17] There is a significant variation between and within different methods of sanitary wear. [18] Grimes reviewed 15 commercially available sanitary products and discovered that mean absorptions ranged from 1.32 to 94.86 ml for different products. [17] A substantial variation in absorbency within specific products was also observed. A history of clot passage is more suggestive of a pathological amount of bleeding as the uterine fibrinolytic system is by definition overwhelmed.

The subjective nature of the complaint has led to attempts to objectify or semi- objectify the menstrual losses of patients. Assessment methods for menstrual loss have been developed. The most commonly used method is the alkaline haematin method devised by Hallberg et al in 1964 [14] or modifications thereof (as described by Gannon et al [19] and Newton et al [20]). These methods are seen as the gold standard and require women to collect their sanitary wear over a cycle (taking care to include all losses – e.g. clots or flooding episodes). Standardised sanitary wear is required. The pads are immersed in a dilute alkali (5% sodium hydroxide). The haemoglobin reacts with the alkali to form alkaline haematin. The haemoglobin content is then assessed by estimation of the absorption of light at 564 nanometres wavelength by the alkaline haematin measured using the technique of light spectrophotometry. The reliability of the test is greatest if completed over two cycles. Limitations exist with this test. It is laborious, unpleasant and time consuming and it relies on the woman collecting all menstrual loss which can be both unacceptable and impracticable. As a result its use remains generally restricted to clinical trial settings. Furthermore it only allows measurement of the haemoglobin content as a surrogate marker of menstrual loss. Fraser et al established that up to 50 – 60% of menstrual loss is not accounted for by whole blood but made up from endometrial transudates. [21] Thus quantification of haemoglobin may not accurately reflect the true losses and underestimate the symptoms. Also the technique does not take into account extraneous losses such as clots falling into the toilet or flooding episodes. It has been suggested that up to 12% of menstrual losses may be extraneous.[22] From a practical point of view when using the alkaline haematin method only certain sanitary wear can be used as modern sanitary wear contains a highly absorbent gel that 'locks away' the menstrual fluid and cause underestimates with the alkaline haematin method.

Pictorial Blood Loss Assessment Charts (PBLAC) have been developed. [23] They attempt to semi-objectify the losses and they are more user friendly than the alkaline haematin method. Patients are required to record on a chart the appearance of their pads or tampons and the number used for each day of their cycle. Episodes of clots and or flooding are recorded. From these charts a score can be calculated with different scores

for pads and tampons. For tampons a score of 1 is given for light soiling, 5 for moderate and 10 if the tampon is saturated. For pads the score is 1 for light soiling, 5 for moderate and 20 for saturation. Clots are scored on a scale 1 (small) or 5 (large). Standardised pads or tampons are required. PBLAC scores over 75 correlate with pathological blood losses giving high sensitivity (86%) and specificity (88%). [23] The weak points of the PBLAC is in the estimation of extraneous losses into the toilet at ablutions, a tendency to underestimate large volume losses and the fact that the sanitary wear on which the data is based is no longer available. The reliability of the assessment has been questioned in a validation study.[24] (See Fig 1)

Fig 1. Pictorial Blood Loss Assessment Chart (Adapted from Higham et al 1990).



A 'Menstrual Pictogram' has been developed. This is similar to the PBLAC method but asks women to estimate extraneous losses (e.g. losses whilst changing protection / during ablutions) and to estimate the absorbency of their sanitary wear. This attempts to correct for extraneous losses (which in high volume losses can be extensive) and the variation in absorbency in sanitary wear.[25] (see Fig 2.) Compared to the PBLAC system there are two additional icons for towels and one additional for tampons. Towels are separated into day and night towels and tampons into regular, super and super plus tampons. In addition there are icons to estimate loss into the toilet and three icons to estimate clots. The score is calculated in millilitres that are equivalent to the actual amount of blood lost. A validation study by Wyatt et al [25] to assess the Menstrual Pictogram verses the gold standard Alkaline Haematin test has been performed .It concluded that there was a significant positive correlation between a women's ability to estimate her blood loss on sanitary wear using the menstrual pictogram and her actual loss as estimated by the alkaline haematin test. In its ability to estimate extraneous losses it proved superior to the alkaline haematin method by allowing the inclusion of these losses. The inclusion increased the objective diagnosis of menorrhagia from 36% of a group presenting with subjective menorrhagia to 74% of this group when extraneous losses were included. It has yet to be validated as a tool used retrospectively and requires standardised sanitary wear.

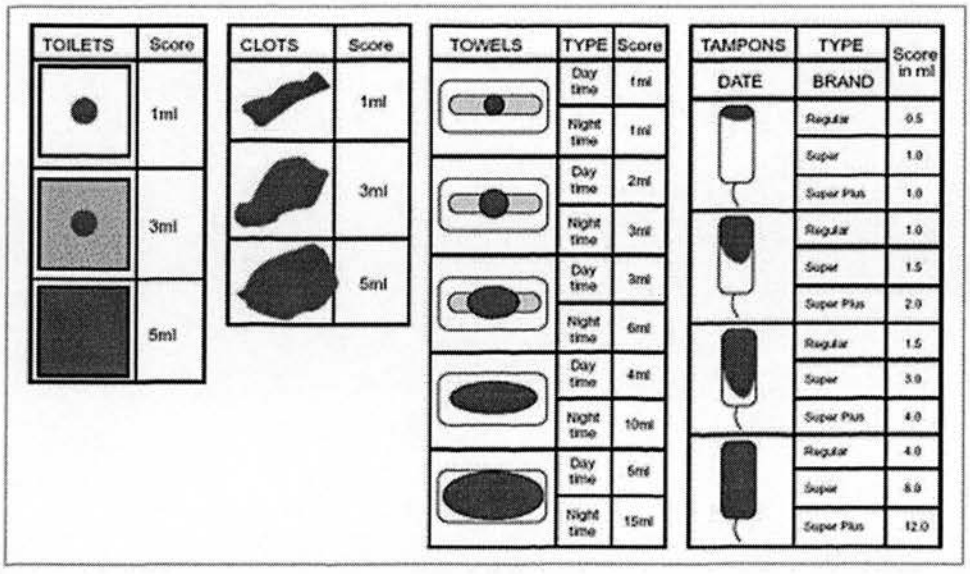


Figure 2. Menstrual Pictogram.

Weighing all sanitary wear can be used as a method of estimating blood loss but again requires collection of sanitary wear and its associated limitations. Also as Fraser et al [21] reported there is a wide variation in the proportion of menstrual fluid that is made up by whole blood from 1.6% to 81.0% (average 36.1%). Thus weight estimates are an inaccurate method of estimation of menstrual blood loss.

Menstrual fluid containment devices such as the Gynaeseal and Menses Cup have been devised .This obviates the need for sanitary wear by collecting all menstrual fluid. Gynaeseal was devised by a Melbourne physician Dr John Cattanach and consisted of a vaginally placed latex device that fitted over the cervix by gentle suction and created a menstrual seal for up to 24 hours. It was assessed by Gleeson et al [26] in 12 women with normal menses and 10 with menorrhagia. Twenty-one of the 22 women found the device easy to insert, but 16 found removing it to be messy. All women with menorrhagia and 4 of 12 women with normal menstrual losses were dissatisfied with the menstrual seal provided by Gynaeseal. The device is not commercially available and has no research role.

A variety of menstrual cups, which fit under the cervix and collect menstrual fluids rather than absorb them, have been manufactured since the 1930s. After insertion the cup molds itself to the individual woman's internal shape, creating a seal that protected against leakage. Acceptability is moderate with 62% at a year reporting it as acceptable in a study by Cheng et al.[27]

The majority of patients will present because their symptoms interfere with aspects of their life (home / work / social / sexual).[28] The fact that the symptom's exhaust their coping strategies is often a precipitant for seeking advice. It is also of note that perceived heavy bleeding and psychological disturbance are weaker predictors of initiation of consultation in primary care.[28] It is also of note that women who present to primary care complaining of heavy vaginal bleeding are more likely to have a psychological disturbance than matched controls[28] and psychological distress increases the likelihood of future reporting of menstrual disorders including menorrhagia.[29]

In summary the complaint of excessive menstrual loss is subjective with often a poor correlation between objective and subjective losses. The objective measurement is restricted to scientific studies and medical or surgical trials and has very little to add in the clinical setting. The objective measurement of a loss less than 80 mls to a patient may reassure a minority but treatments will still be sought by many whatever the quantification revealed.

The primary aims of all treatment is to restore quality of life and alleviate symptoms in a patient centred evidence based approach where the patient makes decisions for treatment based on a knowledge of the relevant options and their pros and cons.

1.1.3 Physiology

The endometrium is divided into a persisting basal layer and a more superficial functional layer. The superficial functional layer is composed of a surface epithelium and complex vascular tree embedded in a connective tissue stroma. The superficial functional layer is destined to become the maternal component of the placenta and its role in the short term is to provide a suitable environment for the implanting blastocyst. [30] If implantation does not occur the falling levels of progesterone trigger the shedding of this functional layer.[31]

The complex nature of the uterine / endometrial vasculature was outlined by Rogers. [32] Within the myometrium the uterine and ovarian arteries form the arcuate arteries which give rise to the radial arteries. The radial arteries on passing the endo-myometrial junction branch into the basal arterioles and the spiral arterioles which supply the basal and superficial functional layers respectively. The spiral arterioles branch extensively in the superficial layer and just below the surface of the superficial layer they form a sub-epithelial plexus that drains into venous sinuses. As the functional layer develops the spiral arterioles become coiled around mid-cycle and span the basal and functional layers. The spiral arterioles are unusual amongst resistance arterioles, in that they lack significant elastin within the internal lamina. [33] Each spiral arteriole provides a blood supply to a uterine luminal surface area estimated at 4-9mm^2. [34]

Compared to the other vascular beds found in the human body the endometrial vascular bed has features that make it unique amongst the vascular beds. [35] No other vascular bed demonstrates growth and regression cycles. The changes in endometrial vasculature at both a macroscopic and microscopic level have been described. The seminal work on angiogenesis in endometrium transplanted into the anterior chamber of a female rhesus monkey allowed direct visualisation of the changes taking place in the endometrium through a cycle. [36] Further work using electron microscopy on timed endometrial

biopsies has revealed an extraordinary array of often well timed changes in the endometrial vascular, cellular and extra cellular components. [37]

Steroid hormones have a key role in the regulatory mechanism of angiogenesis in the endometrium, mediated through their sequential exposure through the menstrual cycle.[35] The endometrium expresses both oestrogen (ER) and progesterone receptors (PR) in both the epithelial and stromal cells. [38;39] Two subtypes of oestrogen receptors {ERα (alpha) and ERβ (beta)} are seen. Two subtypes of progesterone receptor are seen PR A and PR B. [40]The expression of the PR receptor is controlled via the presence of progesterone and oestrogen. In the oestrogen predominant follicular phase the endometrial PR expression is up regulated by the effect of oestrogen on mRNA and protein production. [41] Down regulation occurs through the interaction with progesterone. Progesterone antagonises the oestrogen mediated proliferation of the endometrium through a reduction in ER mRNA synthesis. [33] Membrane actions for both progesterone [42] and oestrogen[43] have been reported. The proportions and concentrations of both PR receptors vary through the menstrual cycle. The total quantity of both types of PR receptor increases in the glandular epithelium during the proliferative phase under the influence of oestrogen and declines in the follicular phase under the influence of progesterone. [44-46]

Oestrogen receptors have been localised using immunohistochemical studies, ERα has been identified in the nuclei of glandular and stromal components. Oestrogen action is dependent upon the presence of specific ligand-activated receptors in target tissues. The expression of ERα increases during the proliferative phase.

Angiogenesis in non endometrial tissue has typically a predictable pattern of endothelial cell activation, degradation and breakdown of the basal lamina, migration and proliferation of the endothelial cells, fusion of sprouts and tube formation. [32;35;47]Angiogenesis in human endometrium appears to differ from this mechanism with proliferating endometrial cells appearing inside existing vessels. Alternative mechanisms for this form of angiogenesis have been proposed. [32;35;48] Critchley et al studied the spatial and temporal pattern of expression of oestrogen receptor beta (ERβ) with that of oestrogen receptor alpha (ERα) in full thickness endometrial samples obtained from both

women and rhesus monkeys. ERα and ERβ were both expressed in nuclei of the glands and stroma. ERα expression declined in the glands and stroma of the functionalis during the secretory phase. The luminal epithelium also displayed positive immunoreactivity for ERβ. Expression of ERβ declined in glandular cell nuclei, but not stroma, within the functionalis during the late secretory phase. Levels of expression of ERα and ERβ in all cellular compartments remained unchanged in the basalis layer when studying the vascular endothelium and the peri-vascular cells surrounding endometrial blood vessels only ERβ was present in the endothelial cell population, although both forms of ER were expressed in peri-vascular cells. They concluded that the action of oestrogen within the vascular endothelium in the endometrium may be mediated via direct binding to the ERβ isoform. [49] The same team also assessed expression of the ERβ variant isoform (ERβcx /β2). This newly identified receptor lacks the ability to bind steroids. ERβ1 and ERβcx /β2 proteins were identified within multiple cell types within the endometrium. The immuno-expression of ERβcx /β2 appeared less intense than that of ERβ1 in endometrial glandular epithelium and endothelial cells. Immuno-expression of ERβ1 appeared unchanged throughout the menstrual cycle. In contrast, levels of ERβcx/β2-specific immunoreactivity were specifically reduced in gland cells within the functional layer, but not in those of the basal layer, in the mid-secretory phase. They concluded it is possible that co-expression of ERβcx/β2 in cells containing ERβ1 and/or ERα may modulate the effects of estrogens on the endometrium.[50]

The mechanism of menstruation is triggered by the fall in progesterone levels, in the absence of a pregnancy, on an oestrogen and progesterone primed endometrium. The use of the anti progesterone Mifepristone (RU 486) has been used to model progesterone withdrawal in menstruation, break through bleeding and early pregnancy loss. [51] The haemostatic response to menstruation differs from the normal tissue responses to a haemostatic challenge. The normal stages of haemostasis characterised by platelet adhesion, aggregation into a platelet plug followed by platelet activation and degranulation combining with fibrin to form a haemostatic plug ultimately progressing to fibrinolysis and clot dissolution is not seen. Instead, the start of menstruation is

characterised by an observed period of intense vasospasm thought to be mediated at least in part by prostaglandin F 2α. Vessel lesions are observed without any of the normal attendant platelet mediated haemostatic reaction. [52] The first 20 hours of menstruation is characterised by the shedding of the superficial functional layer including the vessels and small thrombi. The thrombi are of interest as they are responsible for the majority of haemostasis in the first 24 hours and are usually too small to completely occlude the vessels and achieve an effective platelet plug. They are thus ineffective in reducing the loss of menstrual blood. The fact that the tissues levels of tissue plasminogen activating factor are elevated in women with objective menorrhagia further impacts on the haemostatic challenge. [53]

Prostacyclin has potent platelet adhesion and aggregation inhibition effects that may be responsible for the small and ineffectual platelet plugs seen in the early phase of menstruation.[54]The actual mechanism for the shedding of the functional layer is though to involve the induction of matrix-metalloproteinase (MMP) as summarised by Smith et al. [55] MMP 1,2 and 9 are involved in the up regulation of transforming growth factors β (TGF β) . This results in a denuding of the vessel support and rupturing of the spiral arterioles and venules at the junction between the functional and basal layers. Whilst the spiral arterioles can vaso-constrict their muscularis coat the venules, lacking a muscularis, have to rely on platelet plug and regeneration for haemostasis.

Nitric Oxide (NO) has a number or roles in the endometrium. [56] It exists in two forms endothelial NO and inducible NO.[57] In the menstrual phase the levels of inducible NO rise to six times the levels seen in proliferative or late secretory phase endometrium whereas the levels of endothelial NO remain unchanged.[57] It is an important mediator of vascular paracrine interactions, a powerful inhibitor of platelet aggregation and a potent vasodilator. The over expression of NO in its inducible form may be implicated in menorrhagia. NO is also a neurotransmitter and has a role in apoptosis, a significant process in angiogenesis cycle seen in menstrual endometrium. NO has been implicated in the initiation and control of menstrual bleeding. It also may have a role to play in dysmenorrhoea as it has been seen to suppress myometrial contractility in both the non pregnant and pregnant uterus.[56]

The central haemostatic function after 24 hours is though to be vasoconstriction which reduces the blood loss until ultimately the endometrium regenerates under the proliferative effects of oestrogen. This healing of the endometrial mucosa is not associated with a scar formation and thus is more akin to foetal healing than adult healing.

Prostacyclin may again have a role in menorrhagia as it causes intense vasodilatation. Women with excessive menstrual bleeding attributed to dysfunctional uterine bleeding have demonstrably higher levels of prostacyclin in their menstrual endometrium than controls with normal menstrual blood losses. [58]

Disordered angiogenesis may also have a role. It is observed that the proliferative index of endothelial cell in women with objective menorrhagia is twice that of women with normal menstruation. [55]

1.1.4 Aetiology of Excessive Menstrual Loss

The aetiology of menorrhagia is diverse. The vast majority of women (80%) with this condition have no organic disease and have the label of dysfunctional uterine bleeding. Dysfunctional uterine bleeding may be subdivided into objective, when the loss reaches the 80 mls per cycle threshold, and subjective where the patient complains of heavy bleeding and the loss does not reach the 80 ml threshold.

The aetiology is felt to lie at a cellular level with a complex interplay of the coagulation pathways, prostaglandin, uterine fibrinolytics, vaso-active substances and the uterine vasculature. To date much basic science work remains to be done.

Dysmenorrhoea or painful periods is a common complaint that often coexists with menorrhagia. 79% of patients in a study by Warner et al [59] referred with severe dysmenorrhoea had coexisting menorrhagia. 30 – 50% of the female population are affected.[60;61]The negative effects on a patients quality of life, the impact on health care resources and an impact on the economy through high levels of absenteeism are considerable [60;61]. The main conditions are as follows.

1.1.5 Uterine Fibroids

Uterine fibroids are the commonest tumours affecting women of reproductive age.[62] Up to 1 in 5 women over the age of 30 will have a fibroid.[63] A racial predominance is seen, a higher incidence, earlier onset and greater severity of disease is seen in black women.[64] The exact mechanism whereby fibroids are associated with menorrhagia remains unclear. Theories focus on a change in uterine vascularity, impaired venous drainage, increased endometrial surface area affect and increased expression of prostacyclin. The reason why fibroids are asymptomatic in the majority of women is unclear. What is clear however is that the most common presenting complaint of fibroids is menorrhagia.[65] It is also of interest to note that fibroids are more common in the group of patients with objective menorrhagia. In a study by Rybo et al 43% of women with an MBL of greater than 200mls had fibroids compared to only 10% having fibroids in the group with MBL between 80 and a 100 mls.

A recent paper assessed the effect of size and location of fibroids on menstrual blood loss. [66] This Scottish data analysed 50 women over a three year period whose fibroids were assessed on MRI (all but one) and were on the waiting list for Uterine Artery Fibroid Embolisation.

MBL was calculated using the gold standard alkaline haematin technique. [3]

Fibroid position and volume was assessed on MRI by an experienced radiologist unaware of the MBL results. The majority, 33 (66%) had objective menorrhagia. Of the 42 women complaining of menorrhagia the majority, 33 (79%) also had objective menorrhagia.

With regards to location of fibroids some interesting results emerged. Intramural fibroids were the commonest. The common dictum that menorrhagia is secondary to cavity distortion was challenged as all but two of the women had distorted cavities but 17 had MBL less than 80mls. Of clinical interest all the women with sub- mucosal fibroids had MBL greater than 80 mls. This would be in keeping with the theory that the endometrium overlying sub-mucosal fibroids either functions abnormally [67] or that the

increased endometrial surface area is created by the effect of the sub-mucosal fibroid.[68] The only associated factor to correlate with MBL was the diameter of the largest fibroid.

1.1.6 Adenomyosis

Adenomyosis is a pathological condition characterised by the ectopic location of endometrium in the superficial and / or deep myometrium. The associated heavy menses and secondary dysmenorrhoea may be difficult to distinguish from endometriosis. Clinical diagnosis by the classical globular, tender uterus is unreliable. High false positive rates with ultrasound and to a lesser extent with magnetic resonance imaging means that the condition is often only diagnosed at hysterectomy.[69] Occasional cases are diagnosed at TCRE, on the endometrial chippings and indeed TCRE is a treatment for superficial adenomyosis, but has no benefit for deep adenomyosis. [70;71]

1.1.7 Endometritis

Endometritis is characterised by the presence of a chronic infective or inflammatory process of the endometrium. This is usually polymicrobial in nature and secondary to either ascending pelvic infection or intrauterine manipulation and can result in irregular and excessive menses.

Greenwood reviewed 99 women with chronic endometritis. [72] Clinically 94% presented with vaginal bleeding problems. Histological features were of superficial stromal oedema, increased stromal density, a pleomorphic stromal inflammatory infiltrate (with leucocytes predominating) and the presence of a plasma cell infiltrate in the absence of premenstrual histological changes or other significant pathological lesions. Risk factors were recent uterine instrumentation (curettage or biopsy) and submucous fibroids. The extent of the lesions and the degree of inflammatory infiltrate did not correlate with the severity of symptoms. [72]

Actinomyces infection of an IUCD can also present with menstrual problems.[73] A review of 1500 IUCD / IUS users revealed an average of 11.4 % of IUCD users colonised with Actinomyces and an increased incidence with prolonged use.[74]

Tubercular endometritis is rarely seen now in the developing world but may present with menstrual problems and infertility. A review of 120 cases of genital tuberculosis proved by histopathology revealed 19.0% complaining of menorrhagia. Hypomenorrhoea or oligomenorrhoea were the commonest menstrual symptom in 54.0% of cases whilst amenorrhoea was present in 14.3% cases. [75]

1.1.8 Endometrial Hyperplasia / Neoplasia

Abnormality of endometrial proliferation has been associated with excessive menstruation. Hyperplasia and neoplasia may be associated with abnormal menstrual bleeding and either excessive or irregular loss.

The risk of associated malignancy is very low with simple hyperplasia and complex hyperplasia without nuclear atypia.[71] This has a high spontaneous regression rate in the order of 90% with only 1-3% progressing to invasive disease. [71] Atypical hyperplasia has a regression rate of 60% and a progression to adenocarcinoma of 25%. 20% of atypical hyperplasia has co-existent endometrial adenocarcinoma. [76]

1.1.9 Vascular Anomalies

Arterio-venous malformations (AVM) may occur any where in the body. Uterine AVM can be congenital, acquired through trauma or surgery [77;78]or associated with gestational trophoblastic disease [79]and to date there are less than one hundred case reports in the English language literature. AVM can be associated with severe and life threatening haemorrhages and traditionally has required hysterectomy as a life saving procedure.

The diagnosis can be made through a combination of cautious hysteroscopy, doppler ultrasound and pelvic angiography. In view of the risk of precipitating severe haemorrhage dilatation and curettage are contraindicated where ever AVM is suspected. Successful treatment with selective embolisation of the feeding vessels is the desired treatment [80] and offers a uterus preserving option that is very important as many women will have unresolved fertility desires at the time of diagnosis.

1.1.10 Hypothyroidism

Under activity of the thyroid gland can be associated with excessive menstrual bleeding [81] that responds to thyroid replacement and restoration of a euthyroid state.[82] It is interesting to note however that the most common menstrual effects of thyroid dysfunction is amenorrhoea or oligomenorrhoea.[83] When questioning a cohort of 50 hypothyroid women 56% reported menstrual cycle abnormalities, the commonest being the complaint of menorrhagia.[84] It is recommended in the RCOG Guidelines [85;86] that thyroid function tests are only performed where hypothyroid symptoms exist. It is not cost effective to routinely screen for thyroid disease.

The mechanism is thought to lie in either an effect on LH / FSH ratios and ovulation or possibly a haemostatic defect with a temporary acquired Von Williebrands disease which is reversible on institution of thyroxine treatment. [87;88]

1.1.11 Coagulation Defects

Coagulation disorders can present to the gynaecologist with excessive menstruation often of a dramatic kind, and to the obstetrician with post partum haemorrhage. A study looking at 15 women with known coagulation disorders identified blood losses in the rather dramatic range of 750 – 1000 mls per cycle. [89]

The commonest disorders of coagulation include Von Williebrands, Haemophilia A, deficiency of Prothrombin and Factor deficiencies (V, VII, IX, X, XI)

Anticoagulant therapy can result in an acquired defect of coagulation. Van Eijkeren et al reported on a series of 11 women on oral anticoagulants .[90] The mean menstrual blood loss for the eleven was 98 ml (range, 9 to 239 ml). Six had eumenorrhoea and five women had menorrhagia. Of the six women with normal menstrual blood losses, two had losses in the high normal range (60 to 80 ml). There was no correlation between anticoagulant state and menstrual blood loss. The group suggested that oral anticoagulants increase the trend towards excessive menstrual blood loss. [85]

Severe uraemia may cause altered platelet function and severe liver disease with resultant defects in coagulation factors are also causes of menorrhagia related to coagulation defects in those that are not amenorrhoeic.

The possibility of a inherited coagulation disorder or platelet disorder should be always be considered in those young, often adolescent women referred from their general practitioner with a history of heavy menstrual bleeding from menarche unresponsive to medical treatments. They may give a family history of the condition or allude to other symptoms such as easy bruising and dental bleeding. There is some debate as to the true incidence of coagulation disorders in young women and adolescents complaining of menorrhagia. The often quoted paper by Classen and Cowel [91] from the 1980's retrospectively reviewed all admissions to a children's hospital for acute menorrhagia, where genital tract pathology had been excluded. 59 patients were identified over a nine year period. A primary coagulation disorder was found in almost 20% of these. One quarter of those had severe menorrhagia, one third of those required transfusion, and one half of those presenting at menarche had a coagulation disorder (most commonly thrombocytopenia and Von Williebrands). They concluded that proper screening and therapy are essential in all young women with menorrhagia. A later paper by Falcone et al in 1994 reported, however, a much lower incidence of coagulation / platelet disorder in their retrospective, multi-centre analysis. All adolescents admitted to three paediatric hospitals in Montreal, Quebec, Canada, over a 10-year period (1981-1991) with a primary diagnosis of dysfunctional uterine bleeding were assessed. Sixty-one patients in

total were identified. Only two patients (3%) had an identifiable condition (one with immune thrombocytopenic purpura and one with acute pro-myelocytic leukemia). In contrast to Classen's work all patients who were evaluated had normal factor VIII levels, partial thromboplastin times and prothrombin times. The mean age at presentation was 13.8 +/- 2.1 (SD) years. More than 50% of the patients had a history of irregular bleeding. Most patients (93.4%) responded to medical management with only five (8.2%) requiring therapeutic dilation and curettage. Given the close proximity to the menarche, the preponderance of irregular cycles and the lack of demonstrable coagulation / platelet disorder they concluded that the etiology of dysfunctional uterine bleeding in adolescence is most likely related to the immaturity of the hypothalamic-pituitary-ovarian axis. Of note the vast majority responded to medical therapy which was highly effective in controlling such bleeding. Surgical measures such as therapeutic dilation and curettage were rarely required.

1.1.12 Platelet Disorders

Normal platelet function is an essential part of the haemostatic mechanism in menstruation. It is particularly important after the first 24 hours where platelet plugs in the spiral arterioles and venules are the main mechanism. Platelet disorders in the form of thrombocytopenia, Glazmann's thromboasthenia, Bernard –Soulier Syndrome, Aplastic Anaemia and Leukaemias may present with menorrhagia.[88]

Whether the primary pathology is reduced adhesiveness (Bernard –Soulier Syndrome – a hereditary disease), reduced production (bone marrow failure, infiltration) or increased destruction (hypersplenism, auto immune thrombocytopenia, congenital thrombocytopenia) the end result is a failure of the haemostatic mechanism to the challenge of menstruation.[92]

1.1.13 Intra-uterine Contraceptive Devices

Copper bearing intrauterine contraceptives are effective methods of contraception. They do however have certain negative effects on a patient's menstrual cycle. Inter-menstrual bleeding, an increase in reported dysmenorrhoea and menorrhagia are reported. The foreign body reaction essential to the contraceptive function of the device is implicated in the mechanism of IUCD related menstrual problems. Although the copper IUCD devices have no effect on ovulation they are associated with reduced luteal phase [93] and an earlier onset of menses.[93;94] Menstrual problems from light irregular bleeding / spotting through to heavy and / or prolonged bleeding are commonly reported in the first 3 – 6 month of use of an IUCD but the majority will settle over time.[95] Menstrual bleeding problems and bleeding with pain are the commonest reasons for IUCD removal.[95;96] The incidence of removal for bleeding problems is no greater with the classic versus frameless IUCD.[97] Dysmenorrhoea can be treated with NSAIDS and the heavy bleeding responds to Tranexamic Acid. [85;86]

Ongoing menstrual problems in someone who otherwise prefers an intrauterine device can be remedied by conversion to a hormonal impregnated device such as the Mirena IUS (Schering).

Others Associations

1. Increasing weight, age and number of intrauterine pregnancies have been all associated with increasing menstrual blood volume.[98] The mechanism for increased blood loss with higher parity is thought to be a reflection of the increased uterine size (increased endometrial surface area).The increased loss with age may reflect higher parity and increased BMI.
2.. Body Mass Index. The mechanism postulated is one of higher circulating peripherally produced oestrogens resulting in disturbances of the hypothalamic- pituitary- ovarian axis and anovulation.[99]

1.1.14 Investigations

Patients are assessed clinically with a full medical and gynaecological history. An assessment should be made of the effects of the condition on the patient's quality of life. [85;86] Symptoms of bleeding diathesis (easy bruising / excessive bleeding at dental extraction or in response to minimal trauma) ; hypothyroidism (lethargy / cold intolerance / weigh gain / constipation) ; and anaemia (fatigue / poor exercise tolerance / breathlessness) should be sought. Clinical examination should include an assessment for features of iron deficiency anaemia, hypothyroidism and liver disease. Abdominal, pelvic examination and a speculum are required to assess the size and shape of the uterus. For the purposes of the RCOG guideline the uterus requires to be less than 10 weeks in size. [86] Trans-vaginal Ultrasound Scanning (TV USS) is not indicated with a normal clinical examination and regular bleeding pattern. However, TV USS is useful in the assessment of the endometrium in those with irregular bleeding and in the identification, dimensions and location of any associated submucous fibroids and should be used as the first line investigation of the endometrial cavity. [86]

Patients should all have a full blood count checked to exclude anaemia and thrombocytopenia. Thyroid function tests and coagulation screens should be performed only if clinically indicated. Endometrial sampling can be performed where clinically indicated. The routine histological assessment of women under the age of 40 years is not recommended. [100] The incidence of serious pathology is very low (less than one case per 100000) in the under forty years of age group – such that 3000- 4000 samples would be required to detect one case. [101] Women over the age of forty years, those not responding to first line medical treatment and those at increased risk of endometrial pathology as estimated by risk factors and clinical history can and should be assessed. Women on Tamoxifen therapy; unopposed oestrogen therapy; those who are obese, diabetic, hypertensive; women suffering from anovulatory infertility [especially polycystic ovary syndrome] and those with family history of HNPCC (Hereditary Non Polypoid Colonic Carcinoma) are at a greater than average risk of both pre-malignant conditions such as hyperplasia and of endometrial cancer itself.

The evidence does not support the routine use of dilatation and curettage. The technique is blind, requires general anaesthesia and theatre time. The technique samples between 30 and 50% of the endometrial cavity and whilst this is adequate for global endometrial pathological processes it is poor at detecting focal pathology.[95] Gimpleson et al [102] compared the diagnostic information received from dilatation and curettage following panoramic hysteroscopy in 51 women. For the majority of cases the two procedures agreed with each other however hysteroscopy provided more information in 16 cases whilst curettage provided more information in 2 cases. The procedure has no therapeutic merit (menses return to previous levels or greater after 1-2 cycles) [103] and the fact that it misses significant amount of intrauterine pathology especially localised disease processes such as endometrial polyps and more worryingly early focal endometrial neoplasia is a concern. [100]

Current practice for outpatient endometrial sampling involves the use of endometrial samplers. In the United Kingdom the most commonly used is the Pipelle (Pipelle de Cornier ®, Laboratoire C.C.D, France), a 3 mm manual suction aspiration device. It is well tolerated, cost effective and has a high acceptability and diagnostic accuracy. The RCOG guideline development group felt it was on balance the optimal sampling device.[86] Others do exist and offer benefits but often offset by larger diameter instruments and greater patient discomfort for example the Vacurette Aspirator which has been compared in a RCT to the Pipelle aspirator. [104]

The cavity can also be assessed by transvaginal ultrasound. This is a highly acceptable and versatile tool.[105]The high-resolution images give accurate information about the endometrial cavity. An endometrial thickness of less than 12mm can be used as a screen prior to considering endometrial sampling.[106-109] The current guidelines on Heavy Menstrual Bleeding of the New Zealand College of Obstetricians and Gynaecologists recommends TV USS as the initial screening tool prior to endometrial sampling in those at low risk of endometrial cancer.[110] The diagnostic accuracy of TVUSS can be enhanced by the use of saline infusion hysterography[111-113] . This technique would appear to be especially useful in the differentiation of endometrial polyps and sub-mucous fibroids. Ultimately the gold standard assessment of the endometrial cavity is

hysteroscopy and directed biopsy. The procedure has been shown to be superior to dilation and curettage.[102,114,115]

Hysteroscopy is traditionally performed as an inpatient procedure under general anaesthesia. The technological advancement in fibre-optics, solid state cameras and general miniaturisation of hysteroscopy has allowed the procedure to be performed under local / no anaesthesia as an outpatient procedure.[116] These rigid or flexible micro-hysteroscopes have the ability to provide high resolution, diagnostic images without the requirement of general anaesthesia. As a procedure it compares well with inpatient hysteroscopy, with a very similar failure rate (4% for outpatient hysteroscopy versus 3% at inpatient hysteroscopy)[117] , with women describing the pain as tolerable and less than menstruation.[118] Clark et al assessed the diagnostic accuracy of the investigation in a meta-analysis.[119] A positive hysteroscopy raised the prevalence of endometrial cancer from a pre-test probability of 4% to a post test probability of 72%. A negative result reduces the post-test probability to 0.6%. Hysteroscopy, in particular outpatient hysteroscopy is a growing area of interest. Twenty eight percent of UK gynaecologists when surveyed in 2001 were either performing outpatient hysteroscopy or in the process of setting up an outpatient hysteroscopy service. The British Society of Gynaecological Endoscopists is currently running an outpatient hysteroscopy training course for nurses in a development likely to mirror the evolution of nurse colposcopists. However, there is a note of caution. A randomised trial comparing endometrial biopsy versus endometrial biopsy and hysteroscopy by Bain et al [120] found that the routine use of hysteroscopy did not change clinical decision making, especially with respect to hysterectomy rate. Whilst there were additional pathologies detected they were uniformly benign and detection did not change clinical management. They concluded that hysteroscopy may be useful in selected cases, but when performed in a non-selective manner, it had little influence on clinical management and increased costs.

This finding goes against the rapid expansion and liberal use of outpatient hysteroscopy as a diagnostic tool in the initial, unselected assessment of women with excessive menstrual bleeding. The wide spread use of endometrial sampling in the such women has also recently been questioned.[121]

1.2 MEDICAL TREATMENT

Treatment of the woman complaining of excessive menstrual loss can range from simple reassurance of normality through to major surgery at hysterectomy. A woman's fertility wishes will determine the options open and closed to her. Many treatments will have a contraceptive effect (e.g. COCP), require the use of barrier methods (e.g. Danazol / GnRHa), and require the use of contraception during the reproductive years (e.g. Ablation) or render the patient relatively or completely infertile (Ablation and Hysterectomy).

For many women medical treatments are either desirable (if future pregnancies are being contemplated) or the only treatment option, for example if surgery is either not desired or contraindicated.

In the United Kingdom substantial expenditure is made every year on medical treatment for menorrhagia with up to seven million pounds spent annually, a figure that rivals the expenditure on surgical treatments. [100] There is evidence that the treatments prescribed in the community are often less than evidenced based and this may lead to an increase in recourse to surgery as patients become disheartened by ineffectual medical treatments. [100]

1.2.1 Reassurance

The relative social taboos surrounding menstruation do nothing to objectify menstrual loss. The trigger for many women to seek medical advice is when they reach a point where they can no longer cope or when they notice that their menses have changed relative to what they perceive as normality i.e. greater than previous or indeed less than previous experience – an experience that is unique to them.

The significant subjective element combined with the inability to readily compare blood loss between women results in a relative ignorance of what is defined as normal. Some women seek medical advice in an attempt to objectify their loss and are happy to be told that they are normal. These numbers are relatively small but an important group in that once normality is established no other treatment is required.

Rees described a pilot study where they assessed the effect of a normal measured menstrual blood loss. [122] 17 women with normal MBL (range 15 -60mls) were advised on the normality of their bleeding, their health status and discharged from clinic. At 3 years follow up 14 had accepted the advice and had not received any treatment.

The medical treatments treatment options will now be reviewed.

1.2.2 Non Steroid Anti Inflammatory Drugs

The commonest non-steroidal anti-inflammatory drug Mefenamic Acid (Ponstan, Chemidex, Surrey, England) is taken 500 mg orally three times a day on heaviest days and is a first line treatment for menorrhagia commonly prescribed in primary care.[123]

NSAIDS inhibit prostaglandin synthesis and are also thought to alter favourably the balance between vasoconstrictor and vasodilatory prostaglandins.

Mefenamic Acid is an effective drug with a 25% reduction in menstrual loss by 75% of women. It is well tolerated in healthy individuals with a good safety profile. Interestingly in a paper by Fraser et al which demonstrated between a 20% and 39% reduction in menstrual blood loss, some women exhibited an increase in their MBL on Mefenamic Acid.[124] Why this group of women experienced an increased blood loss is unclear but an adverse effect on platelet aggregation is postulated.

Its use is restricted in those with a hypersensitivity to NSAIDS (a minority of asthmatics), women with active or previous peptic ulcer disease and severe renal disease. It relieves coexisting dysmenorrhoea in 75% of women, is non-hormonal and non contraceptive. As its use is limited to days of heaviest bleeding this reduces adverse effects and enhances compliance. Mefenamic Acid can be taken in conjunction with Tranexamic Acid. It is also useful in the reduction of menorrhagia associated with non-

medicated intrauterine contraceptive devices. The main adverse effects are gastrointestinal effects, rash, renal impairment and exacerbation of asthma in predisposed NSAID-intolerant asthmatics.

A Cochrane review of NSAID in the management of menorrhagia by Lethaby et al has been reported. [125] Sixteen RCT were involved in the meta-analysis of individual NSAID with each other, placebo or other medical treatments in women with regular dysfunctional uterine bleeding. Weighted mean differences for continuous outcomes were estimated from the data of comparable nine trials. NSAID were more effective than placebo at reducing heavy menstrual bleeding but less effective than either tranexamic acid or danazol. There was a non significant trend towards greater efficacy of NSAID compared to oral progestogen (luteal phase) and ethamsylate but no differences were demonstrated between NSAID and the progesterone releasing intra-uterine system (IUS) and the oral contraceptive pill, although these results were based on very small studies. There was no evidence of a difference between the individual NSAID (naproxen and mefenamic acid) in reducing HMB. NSAID reduce heavy menstrual bleeding when compared with placebo but are less effective than either tranexamic acid or danazol. There were no significant differences in efficacy demonstrated between NSAID and other medical treatments such as oral progestogen given in the luteal phase, ethamsylate, oral contraceptive pill and the progesterone releasing IUS. [125]

The majority of evidence for the role of Mefenamic Acid in menorrhagia comes from small, short (3 months) cross over trials where individual groups acted as their own controls.

1.2.4 Tranexamic Acid

Tranexamic Acid (Cyclokapron, Pharmacia and Upjohn, UK) is one of the most effective medical treatments for menorrhagia. Despite being known of for over thirty years the drug has been reported as the least prescribed medical treatment for menorrhagia in the UK [123;126] making up only 5% of GP's prescriptions. These figures from the mid 1990's have been improved upon by UK evidence from the end of that decade showing that specific evidence based educational packages increased prescribing rates from 32% to 57%. [127] The treatment has been used for many years in Scandinavian countries but has achieved less favour in the UK. Possible explanations lie in the theoretical concerns that a medication that inhibits clot dissolution may promote venous and arterial thrombo-embolism in patients. The concern regarding thrombo-embolism has prevented its licensing in the United States. Long term epidemiological data from Sweden is reassuring on this point revealing that the incidence of thrombosis in women treated with tranexamic acid is comparable with the spontaneous frequency of thrombosis in women not taking tranexamic.[128] The drug is prescribed in the dose of 1 gram orally three times a day for the heaviest days. Tranexamic Acid is a plasminogen activator inhibitor (antifibrinolytic) that has affinity for the five lysine binding sites of plasminogen preventing activation of plasminogen to plasmin thus promoting coagulation in the endometrial vessels. As a treatment it reduces menstrual blood loss by up to 50%.

Women with menorrhagia have been shown to have increased levels of plasminogen activator enzymes [Tissue plasminogen activator enzymes(t-PA)] in their endometrium when compared to women with normal menstrual loss[129-131]. Plasminogen activator enzymes encourage clot dissolution, thus promoting menstrual bleeding. [132,133]

A previous personal history of a thrombo-embolic event is a contraindication to treatment. The treatment is non-hormonal and non contraceptive and can be used by women who are trying to concieve. As use is limited to days of heaviest bleeding this reduces adverse effects and enhances compliance. Tranexamic Acid is also effective in

the reduction of menorrhagia associated with non-medicated intrauterine contraceptive devices. [132]

Randomised controlled trials comparing Tranexamic Acid (or its pro drugs) to placebo [133;134], luteal phase progesterone [135] , Mefenamic Acid [53] , Flubriprofen and Ethamsylate [53]have been published. These trials whilst differing in methodology are generally small trials (participants vary between 20 and 103), are short term (2-3 months of active treatment) and only included women with objectively defined menorrhagia (> 80mls blood loss). They all revealed a significant reduction in menstrual blood loss by Tranexamic Acid varying between a 36 to a 53% reduction. It is interesting that many of the trials reported no significant difference between treatments in terms of subjective reduction in menstrual loss.

The Cochrane Database of Systematic Review entitled 'Antifibrinolytics for heavy menstrual bleeding' assessed the available evidence for the use of Tranexamic Acid [136] and performed a meta-analysis on the suitable trials. The most recent reassessment in April 2004 revealed no new trials of note. Of the 15 trials assessed they concluded that 4 were suitable for meta-analysis. They concluded that antifibrinolytic therapy causes a greater reduction in objective measurements of heavy menstrual bleeding when compared to alternative oral treatments (placebo, NSAIDS, oral luteal phase progestogens and ethamsylate). However they note that although there was a trend towards a greater perceived reduction in menstrual blood loss in the Tranexamic Acid treated groups that this was not significant. Tranexamic Acid uses was not associated with greater reported sided effects when compared to luteal phase progesterone [135] or a greater reported discontinuation rate than with ethamsylate or mefenamic acid. [53] Symptoms of flooding, leakage and sex life were significantly improved after tranexamic acid therapy when compared with oral luteal progestogens. [136]

Of note there is a definite lack of data on the continuation rates and outcomes with long term tranexamic acid treatment, limited quality of life data beyond the work of Preston et al [135], a lack of data on the clinical effects on women without objective menorrhagia (a significant clinical entity) especially as Preston et al reported the most significant

clinical effects with MBL of 80 -200mls and a lack of data comparing Tranexamic Acid with Mirena.

1.2.5 Combined Oral Contraceptive Pill

The use of the combined oral contraceptive pill (COCP) as a treatment for menorrhagia is well established. The use is especially valid where a patient also requires effective contraception. The COCP suppresses, via a feedback loop, the pituitary production of gonadotrophins. The main effect in menorrhagia is through endometrial suppression with a reduction in mean blood loss of approximately 50%. [124; 137] Lighter withdrawal bleeds, reduced dysmenorrhoea and good cycle control are benefits. The COCP can also be tri-cycled (three packets run together) to limit patient to five or six bleeds a year. Epidemiologically the COCP demonstrates a protective effect for endometrial and ovarian cancer and also reduces benign breast disease. Previous concerns regarding use in older women have been allayed and women aged over 40 years in absence of venous or arterial risk factors can continue or commence the COCP. The evidence for the beneficial effect of COCP on menorrhagia is restricted to 30 microgramme pills.

The main contraindications to treatment are risk factors for arterial or venous thrombosis: obesity; hypertension; severe varicose veins; familial thrombophillias and severe or focal migraine.

In general treatment is well tolerated by the majority. Adverse effects include migraine, hypertension, venous thrombosis (greatest with the third generation progestogens desogestrel and gestodene), arterial thrombosis (risk increased by smoking, age and obesity), bloating, weight gain, breast enlargement, breakthrough bleeding and nausea.

The evidence for the use of COCP in the treatment of menorrhagia has been the subject of a Cochrane Review [138]. Iyer et al reviewed the literature originally in October 1996 and most recently in June 2004. They identified only one trial by Fraser and McCarron who randomised 45 women with ovulatory menorrhagia to 3 treatments - Mefenamic Acid, COCP, low dose Danazol and Naproxen. They received therapy with mefenamic acid in 2 cycles and 1 of 3 other agents in 2 cycles (allocated by random). The treatment

was not blinded nor was it placebo controlled. Menstrual blood loss was measured in 2-4 control cycles and during therapy. There was a 43% reduction ($p< 0.001$) reduction in menstrual blood loss in the COCP arm, a 49 % ($p = 0.006$) reduction in low dose danazol arm, a 38% reduction in the pooled Mefenamic Acid arm ($p<0.001$) and a 12% reduction in the Naproxen Arm. There was no significant difference in blood loss reduction observed between the four treatments. Interestingly some in the Mefenamic Acid group had an increased loss and patients who failed to respond to treatment had low pre treatment measured blood losses.

The small numbers of patients in the trial combined with the 15% (7/45) drop out hamper the interpretation of the trial. Ideally an arm with Tranexamic Acid would have enhanced the findings. The data for the COCP in this trial is based on only 6 individuals. To date an adequate RCT comparison of the COCP is required to establish the role of the COCP in heavy menstrual bleeding.

1.2.6 Oral Progesterone

Oral progesterone in the form of the C19 nortestosterone derived progesterone norethisterone (NET) [Primulot N, Schering Health, UK / Utovlan, Pharmacia, Pfizer Ltd, UK], the C21 groups of medroxyprogesterone acetate (MPA) [Provera, Pharmacia, Pfizer Ltd, UK] and are commonly used medical treatments for menorrhagia. In general they are well tolerated and have an acceptable side effect profile.

Progesterone and norethisterone in particular, are the most commonly prescribed oral medication for menorrhagia in the UK. In 1995, norethisterone accounted for 55% of all prescriptions for heavy menstrual bleeding [126]. The management of menorrhagia guidance produced by the NHS Centre for Review and Dissemination published in Effective Health Care Bulletin highlighted the significant lack of evidence based prescribing.[100]

The commonly used dosage regimes are norethisterone 5 mg two to three times a day orally, days 5–25 of cycle and medroxyprogesterone acetate 5–10mg twice a day orally.

The mechanism of action is to stabilise the endometrium in a pseudo-decidualised form. Withdrawal of progesterone from an oestrogen primed endometrium triggers predictable bleed, whereas continuous use causes endometrial atrophy.
There are few contraindications to progesterone therapy but these include severe liver and renal disease.

The main benefits are a reduction in menstrual blood loss (if used in long cycle regime), regulation of a disordered cycle and the balancing of the oestrogenic effect in those who are anovulatory (endometrial protective effect).

The chief side effects are either premenstrual symptoms or androgenic symptoms. Fatigue, mood changes, weight gain, acne, nausea, bloating oedema, headaches, depression, loss of libido, irregular bleeding and, on long-term therapy atherogenic changes in the lipid profile.

It is of note that luteal-phase support, short-cycle regimens; for example, from day 15 to day 26 or day 19 to day 26 are ineffective in the treatment of menorrhagia and, in fact, have been shown to increase menstrual loss. [110]

1.2.7 Levonorgestrel Intra Uterine Device (LNG-IUS)

The LNG-IUS or levonorgestrel intrauterine device (Mirena, Schering Health, UK) is without doubt the most significant advance in the non-surgical treatment of menorrhagia in recent times. The device itself is a T shaped plastic frame onto the long arm of which is a mix of Levonorgestrel (54 milligrams) with polydimethylsiloxane which releases 20 micrograms of the 19-nortestosterone-derived progestin levonorgestrel per day through a rate limiting membrane. The initial rational behind the progesterone releasing device was to add progesterone to an intrauterine contraceptive device (IUD) to reduce the rate of expulsions. The device itself was initially licensed in 1995 in the United Kingdom as a contraceptive, in 2002 it gained a licence to be used in the treatment for idiopathic

menorrhagia and in more recently in 2005 it gained a license for the endometrial protection with systemic oestrogen replacement therapy in peri-menopausal and post-menopausal women. As a contraceptive it is currently used by around 1% of 16-49 year olds using contraception in the UK.[139] Initial studies comparing the LNG-IUS to copper bearing IUCD reported a decreased menstrual blood loss and decreased dysmenorrhoea in women in the LNG-IUS arms. [140;141] The device is suitable for the majority of women who present with menorrhagia and after appropriate counselling and pre – fitting investigations can be fitted and utilised. The device last for 5 years and after that can be refitted. It is contraindicated in : thrombo-embolic disease (in the scenario of current deep venous thrombosis or current pulmonary embolus) , ischaemic heart disease; active viral hepatitis; severe decompensated cirrhosis, benign liver tumours and malignant hepatomas; current breast cancer, current endometrial cancer, current cervical cancer, current trophoblastic tumour and current pelvic infection. [142]

The local delivery of the androgenic progesterone levonorgestrel to the endometrium results in high local levels of progesterone and low systemic levels. The intrauterine levels of levonorgestrel are 1000 times that seen with systemically delivered sub dermal progestogen implant devices.[143] The device is as effective a contraceptive as modern IUD's with a failure rate of less than 1 per 100 woman- years (Pearl Index of 0.18 per 100 women-years). [144]

The high local levels of levonorgestrel result in a variety of observable physiological and histological changes. The predominant histological effect is endometrial atrophy which appears to increase from an initially patchy effect to a more global effect with time. [145] There is also observed an increase in local inflammatory cells seen with IUD in general. [146] Pakarinen et al [147] reported a change in the composition of the endometrial stroma. The stroma of nine fertile women was analysed using scanning electron microscopy over a 6 month exposure to LNG IUS. The glandular epithelial cells became lower; the junctional complexes between epithelial cells remained unchanged, whereas the lateral microvillus inter-digitations became more prominent. The basal lamina under the epithelium became wavy but remained uniform and the stromal cells were largely decidualised. They concluded that in parallel with the generally known cellular effects,

the use of the LNG IUS results in distinct changes in the basal lamina between the endometrial epithelial and stromal cells and that these changes may be involved in the mechanism of the LNG IUS-induced endometrial suppression.

A reduction in the numbers of spiral arterioles is also reported. [148] At a receptor level both the oestrogen and progesterone receptors are down regulated. [149] The hyopathalimc – pituatry – ovarian axis is relatively unaffected with over three quarters of women continuing to ovulate. [150]

The effects of LNG-IUS with respect to menstrual loss reveal a significant effect. The LNG –IUS is the most effective medical treatment currently available. There is over a 90% reduction in menstrual blood loss with approximately one in ten reporting amenorrhoea at one year.[151;152] Side effect of the device reported include hormonal related side effects such as bloating, breast tenderness, acne, headache and menstrual irregularities. The incidence of hormonally related side effects with long-term usage of the LNG-IUS has been compared to standard copper containing IUD and they showed no difference in a randomised controlled trial at 5 years. [153]

Irregular bleeding is cited as a common reason for discontinuation where LNG- IUS is used for menorrhagia. The mechanism for irregular bleeding is not conclusively explained and remains a common cause for discontinuation. Discontinuation rates with LNG-IUS have been compared to IUD in the contraceptive use of the device, this is a different population of users than those complaining of menorrhagia but some interesting features are noted. LNG-IUS users were more likely than other IUD users to discontinue because of hormonal side-effects or menstrual disturbance. No other significant differences in reasons for discontinuation were observed. [153]

Irregular bleeding with the LNG-IUS is common especially in the first three months of use. Proposed mechanisms for irregular bleeding include : endometrial atrophy with patchy atrophy commonly seen in the first three months and more complete atrophy thereafter ; decreased expression of VEGF(vascular endothelial growth factor) and increased expression of Adrenomedullin (AM) in the endometrial glands and

stroma.[154] Results obtained suggest that the increase in AM expression in the endometrium may be responsible for the frequent occurrence of irregular bleeding during the initial 3 months of LNG-IUS.[155] Rogers et al [154] assessed VEGF expression and BVD (Blood Vessel Density) in women complaining of break through bleeding using various hormonal regimes and the Mirena IUS. They concluded that unopposed progestogens reduce endometrial BVD and that there was no link between VEGF immunostaining and BVD or break through bleeding.

Critchley et al reported a study examining endometrial tissue in 14 normal women from insertion of a Mirena IUS through to 12 months post-insertion. ER and PR (A+B) and PR subtype B were significantly down-regulated in glands and stroma in the presence of continuous intrauterine LNG delivery. There was an apparent increase in PR (A) immunoreactivity in endometrial glands between 6 and 12 months post-insertion. The significant suppression of PR (B) implies that the PR (A) receptor is responsible for the long term effect on the endometrium. They concluded that alterations to normal sex steroid receptor expression, following exposure to high concentrations of local LNG, may play a role in the aetiology of bleeding disorders associated with the LNG-IUS.[149]

Matrix Metalloproteinase have important functions in the endometrium. Metalloproteinase-9 (MMP-9) has been implicated in the irregular bleeding seen in some LNG-IUS users. MMP-9 protein is present throughout the cycle with highest expression in glandular cells during the mid-secretory phase. In women with a levonorgestrel intrauterine system (LNG-IUS) MMP-9 is highly expressed in endometrial glandular cells, stromal cells, endothelial and peri-vascular cells. It can be concluded that MMP-9 is stimulated directly or indirectly by progesterone. The increased expression of MMP – 9 and its role in the remodeling of the endometrium during the menstrual cycle may, through associated morphological changes, have a role in the breakthrough bleeding associated with long-term progestogen administration via a LNG-IUS. [156]

The menstrual benefits of the LNG-IUS were first seen in the Scandinavian countries where it was first used as a contraceptive. Andersson et al [151] in a Swedish study of 20

women with confirmed objective menorrhagia and no demonstrable gynaecological pathology who received a LNG-IUS. Menstrual blood loss (MBL) was measured in two consecutive cycles prior to device insertion, and at 3, 6 and 12 months of use. MBL was significantly reduced after 3 months (86%) and after 12 months the reduction was 97%. A significant increase in serum ferritin during the first year of LNG-IUS use was also seen. In a Scottish study Irvine et al [152] used a randomised comparative parallel group study to comparing LNG-IUS to high dose Norethisterone (5 mg / tds) day 5-day 26 in women with objective menorrhagia of a dysfunctional type. The main outcome measure was the change in objectively assessed menstrual blood loss after three months of treatment. The levonorgestrel intrauterine system reduced menstrual blood loss by 94% (expressed as a percentage of the original loss) and oral norethisterone by 87%. There were high rates of continuation with 76% of the women in the levonorgestrel intrauterine system group wished to continue with the treatment, compared with only 22% of the norethisterone group.

A comparison between LNG-IUS and endometrial ablative technologies will be made in the Chapter on surgical management of menorrhagia.

1.2.8 Danazol

Danazol (Danol, Sanofi-Synthelabo, UK) in a dose of 200 mg orally 1–3 times a day can be used successfully in the treatment of menorrhagia as a second line agent. Reductions in measured blood loss by between 30% and 70% are seen with amenorrhoea usually seen in doses of 400 mg/day and above.[157] It was introduced as a medical treatment for endometriosis and commonly used in the treatment of menstrual pain and excessive menses in the 1980's but its popularity has waned.[157-159]

Pharmacologically danazol is an isoxazole derivative of 17 alpha-ethinyl testosterone and as such is a weak synthetic androgen. A complex combination of effects is seen with suppression of GnRH pulse frequency thereby reducing pituitary gonadotrophin production, inhibition of ovarian steroidogenisis and a direct endometrial suppressive effect.[160] The androgenic effects are mediated by the affinity of danazol for the androgen

receptors, its ability to increase the free androgen index by displacing testosterone from sex hormone binding globulin and its ability to reduce the levels of sex hormone binding globulin itself. Anti-androgenic, androgenic, anti-oestrogenic, oestrogenic, anti-progestogenic and progestogenic effects are observed in different tissues. It has multiple uses beyond menorrhagia including in the treatment of endometriosis related dysmenorrhoea, cyclical mastalgia and also as an endometrial thinning agent prior to endometrial ablation / resection. The main contraindications are thrombo-embolic disease, severe cardiac, renal and liver disease, porphyria and uncontrolled hypertension. It is diabetogenic through a reduction in insulin resistance and should be avoided in diabetics.

Prolonged treatment with danazol is limited by the presence of significant adverse effects in women when given in high doses and in prolonged (over 6 months) courses. Androgenic effects predominate. Weight gain, acne, bloating, skin rashes, an atherosclerotic lipid profile, hirsuitism, voice changes and in prolonged use virilisation has been reported. The risk of virilisation of a female foetus necessitates the use of barrier methods of contraception. Despite its significant efficacy many patients are unable to tolerate any more than short term use with high numbers discontinuing treatment due to side effects. It is currently only licensed as a second line therapy.

1.2.9 Gonadotrophin Releasing Hormone Agonist Analogues

Gonadotrophin-releasing hormone analogues (GnRHa) are a useful second line treatment utilised in the medical treatment of menorrhagia. Following an initial stimulatory (agonist) phase lasting 7 – 10 days, there follows a down regulation of the pituitary GnRH receptors, LH and FSH production reduces and a pseudo-menopausal state created with suppression of ovarian steroid hormone production and thus suppression of the endometrium. The initial agonist phase is associated with often an increase in menstrual symptoms of bleeding and, or pain which abate thereafter. It has been used as a short term measure to relieve menstrual symptoms, as a means of down sizing fibroids pre-operatively, as diagnostic tool in the evaluation of chronic pelvic pain

and as an endometrial thinning agent prior to ablation or resection. In those whom surgery is contraindicated it may be useful in the medium to long term.

The main contraindications are osteoporosis and barrier contraception must be utilised to prevent pregnancy. As these are implants or depot injections there are no tablets to remember and this allows enhanced compliance although short term discomfort or bruising at injection sites is common. Treatments are usually monthly to 5 weekly. High levels of amenorrhoea are achieved by second to third injections with a significant reduction in dysmenorrhoea seen.

Complete resolution of associated dysmenorrhoea and pelvic pain gives a good indication of the therapeutic effect of hysterectomy in cases where these symptoms coexist or predominate.

Menopausal symptoms secondary to the induced hypo- estrogenic state are common with vasomotor-type symptoms and vaginal dryness described. An irreversible osteoporotic effect is seen if treatment is continued for longer than 6 months. Add back hormone replacement therapy in the form of combined preparations or the gonadomimetic Livial (Organon, Cambridge, UK) may be used if treatment past 6 months is required or if menopausal effects become a problem.[161-163]

The problems of loss of bone density and high costs of GnRH analogues limit its long term use.

1.2.10 Conclusion

Significant amounts of NHS expenditure are made on medical treatments for menorrhagia. There is a lack of evidence based prescribing in primary care.[123] Educational packages can improve the incidence of evidence based prescribing and reduce referrals to secondary care with its possible knock on effect on the incidence of surgery. [127] The data pertaining to medical treatments varies in quality. Many of the trials of oral therapy are based on small numbers, relate to only 3-6 cycles using a cross

over design to allow different arms to become their own control. Many of the trials, as part of the inclusion criteria, include only those with objective menorrhagia. This has its merits but does increase the difficulty of recommending evidence based therapy to the majority of women who complain of subjective menorrhagia. There is little research evidence from where we can advise this significant clinical group of women. This was borne out in Fraser et al whose randomised crossover trial revealed women with objective menorrhagia having better outcomes compared to those without. [124]

The importance of effective medical treatments cannot be over estimated. The prescribing of ineffective regimens will lead to patients despair and a possible unnecessary resort to surgical treatment. The increased use of tranexamic acid, the most effective oral medication, and of the LNG-IUS, the most effective medical treatment, has to be encouraged. The LNG-IUS is currently the single most important breakthrough in the medical treatment of menorrhagia.

Looking to the future there requires being a greater emphasis on the basic science of menorrhagia especially at the level of gene expression. Preliminary work on proteonomics reveals a potential window to the mechanism.[164] Proteomics is the study of proteins in order to understand cell behaviour. It studies the translation process of RNA into proteins as well as the overall process of DNA into proteins. Proteonomics analysis involves running samples through a 2-D gel electrophoresis. Proteins are then separated by their characteristics of molecular weight, shape, and charge, and expression levels are determined by the resulting patterns on the gels. The expression of different proteins in health and disease states can then be determined and compared. It is suspected by many experts in the field that the central process at the heart of the majority of menstrual disorders is abnormal gene expression.[165] Currently the majority of investment and research is channelled into evermore methods of destroying the endometrium primarily through endometrial ablation. This represents the necessity of commerce driven research to generate income. More funding is required in the less

commercially desirable area of investigating the genetic basis of excessive menstrual loss with a view to targeted gene therapy.

1. 3 SURGICAL MANAGEMENT OF MENORRHAGHIA

The first description of surgery to remove the uterus was described over 2000 years ago in Greek manuscripts.[166] The first and usually fatal attempts at vaginal hysterectomy are recorded from the 16th century.[167] The first description of abdominal hysterectomy comes from Charles Clay of Manchester in 1843 who performed a subtotal procedure, unfortunately the diagnosis was wrong and the patient died.[167] The total abdominal hysterectomy as we know it today was introduced in 1929 by the American surgeon Richardson.[167]

Until the introduction of the first generation, hysteroscopic methods of endometrial laser ablation (ELA) and trans-cervical resection of the endometrium (TCRE) in the late 1980s a hysterectomy by the abdominal or vaginal route was the only definitive surgical treatment for dysfunctional uterine bleeding (DUB). Despite hysterectomy being the mainstay of gynaecology surgery (becoming ever more common with a doubling of the hysterectomy rate in Scotland between 1961 and 1984 [1]) there was little evidence from randomised control trials regarding its role, patient acceptability and long term implications. Some evidence regarding the effectiveness of hysterectomy was already available. Observational studies had shown that though patient satisfaction following hysterectomy was high but not the 100% that many gynaecologists assumed.

The endometrial ablative methods gave the promise of replacing hysterectomy with a minor, quick and safe technique. The endometrial ablative techniques all shared a common aim, to destroy or remove the basal endometrial glands thereby creating a therapeutic Ashermann's Syndrome. In pharmacologically prepared endometrium the basal glands lie at a depth of 4mm and thermal injury or resection requires penetration to this depth [168;169]. The resulting eumenorrhoea (normal periods), hypomenorrhoea

(reduced periods) or amenorrhoea (absence of periods) is the clinical effect. The restoration of normal menses is ultimately the goal.

Historically ablative techniques began in the 1980's with work by Goldrath in the United States (US) on Endometrial Laser Ablation (ELA) [170]. Davis introduced ELA into Britain with the neodymium-YAG laser [171]. In the late 1980's Magos introduced Transcervical Resection of the Endometrium (TCRE) to the British system [172]. A rapid expansion of TCRE in Britain followed. The equipment was initially a modified urological resectoscope, which was easily available in most hospitals. The lack of capital expenditure and general availability of necessary accessories such as bipolar electrosurgical generators and urological glycine enhanced the development of the technique in the UK.

These first generation ablative techniques comprise TCRE, ELA and Rollerball Endometrial Ablation (RBEA). TCRE is the commonest first generation technique in the UK [173], whereas in the US, RBEA is the most common. The expansion of ELA was probably limited by both the significant expense of the laser generator and the specialist training required for the theatre staff.

The early 1990s was a time when the concept of evidence based medicine was becoming established. This meant that the newly introduced endometrial ablative methods were rigorously assessed with randomised controlled trials comparing them to hysterectomy, medical treatment and the differing methods of ablation. Evidence regarding all the surgical methods including hysterectomy began to accrue.

At the same time national audits of endometrial ablation, and recently hysterectomy gave robust data regarding safety.

Despite the increasing acceptance of the role of randomised trials and the concept of grading evidence as used by the Scottish Intercollegiate Guidelines Network (SIGN) it is unfortunate that even to this day the majority of publications in this area are uncontrolled observational studies. Furthermore only the minority of studies have used power calculations to determine the size of the population studied.

A problem with studies on surgery for DUB is the question of outcome measures. Of the patient centred outcomes patient satisfaction is the most useful and important measure and this allows for valid comparison between ablation and hysterectomy. Acceptability is similarly an important patient centred outcome, a procedure can be highly effective but if patients find it totally unacceptable it is of little use. Hysterectomy rates in women treated by conservative surgical methods allow for important comparisons between ablative techniques. Hysterectomy rates are meaningless when comparing ablative techniques with hysterectomy. Amenorrhoea rates are useful when comparing one ablative method with another, but again meaningless when comparing ablation to hysterectomy. Surrogate measures of menstrual loss have their limitations as even the PBLAC score has been shown to be potentially unreliable in women with DUB [24]. Economic outcomes secure data on both direct and indirect costs. Economic analysis, increasingly reported in clinical papers, gives important information for the health service especially if taken over the long-term.

Patient selection for trials and studies is an area where bias is possible. Certain prognostic factors for the success or failure of endometrial ablation have been recognised. Success is more likely in women who are older, have genuinely heavy periods and who have less dysmenorrhoea. [174] Studies can therefore be biased if the trial population is not representative of the population to which the technology will be applied. Care must therefore be taken when interpreting results of studies, especially those that are not randomised. Inclusion and exclusion criteria based on PBLAC scores and the demonstration of genuine menorrhagia, where only women with small regular cavities are included, will give over optimistic results when compared to trials that take a more pragmatic approach with limited inclusion and exclusion criteria that more accurately reflect clinical practise.

1.3.1 Morphological and Cytological Effects

The effects of endometrial ablation have been studied. The evolution of the histological and morphological changes may explain the clinical evolution of treatments post ablation.

Hawe et al [175] describe the immediate post ablation changes using an enzyme histochemical staining technique for respiratory enzymes. They assessed the effect of varying ablation times with the Cavatherm Endometrial Ablation System and the effect on the immediate zone of thermal necrosis (ZTN) and serosal temperature. The temperature was measured with thermocouples at the serosa. The serosal temperature sensors did not demonstrate any rise in temperature above 44.1 degrees C. The maximum ZTN was greatest for the 15-min treatment time (3.1 mm, SD 1.5) compared to the 10- and 7-min treatment times (3.0 mm, SD 1.4 and 2.2 mm, SD 0.7, respectively). The maximum ZTN recorded was 5.6 mm. No full thickness injuries were demonstrated.

Colgan et al describe the histopathological features of the endometruim post electrosurgery in a group of 19 women at three to sixteen months post rollerball endometrial ablation.[176] Of the patient studied at three months or less (n = 6) all displayed necrotic myometrium, and in five of these cases, a foreign body and granulomatous reaction to the necrotic myometrium was seen. Acute inflammation was evident in all six cases but seen exclusively in one case. Examination at three to sixteen months or more post treatment revealed the necrotic reaction had been replaced by a granulomatous reaction and or foreign-body reaction in 5 of 12 cases. In most cases (9 of 12), there was very obvious endometrial scarring. They commented on the similarity between the morphologic response of the endometrium to electrosurgical endometrial and that reported previously for both resection and laser ablation.

Jarvela et al [177] displayed a rise in uterine artery impedance measured with colour flow doppler at 6 months post ablation. Jarvela suggested post operative cavity fibrosis as the mechanism for the change in impedance. The same group also described the ultrasound changes displayed post ablation with a clear and limited hyperechogenic zone surrounding the uterine cavity with or without an area of fluid.[178]

Mishra et al [179] describe and compared the early cytomorphological and histomorphological changes post thermal ablation. They compared three groups – non ablated hysterectomies as a control, hysterectomy specimen's ablation in vitro and hysterectomy specimens ablated in vivo. They describe a characteristic post ablation cytomorphology consisting of fragmented glands, single cells with fuzzy cytoplasm and giant cells. When assessing oxidative enzymes over 90% of endometrial cells from uteruses ablated in vivo compared to 100% of those ablated in the control group.

MRI features post ablation have been described by Olson et al .[180] They performed T1 and T2 sequences on the uteruses of 15 women undergoing MEA. The women were scanned pre-operatively, on the 1st post operative day and at 4 months. On the first post operative day a low signal intensity band was seen subjacent to the treated area of the endometrial cavity on T2 images. At 4 months there was no change in the myometrial or uterine dimensions and significant amounts of endometrial tissue were seen in 11 patients. This included the patients who were amenorrhoeic. The MRI data puts paid to the suggestion by some that unopposed oestrogen HRT is safe in those who are amenorrhoeic.

1.3.2 When to offer surgical treatment for DUB

When hysterectomy was the only surgical option for the treatment of DUB it was seldom employed as a first line treatment. It was standard practice for patients to "earn" their operation by being treated with multiple medical treatments and uterine curettages. Only after these had failed was a hysterectomy employed. This was sensible as hysterectomy is a major procedure not without risks. As the endometrial ablative methods were thought of as an alternative to hysterectomy the same view was held.

Surgical methods, hysterectomy and ablation should only be offered to women who have completed their family, because the absolute sterility caused by hysterectomy and the relative sterility and possible risks of pregnancy following ablation. In couples not using a permanent method of contraception female sterilisation can be offered at the same time as conservative surgical measures.

Data regarding the place of medical versus primary surgical treatment for DUB comes from the original and follow-up papers of a randomised trial comparing oral medical treatment with TCRE[15;181;182] and from trials of Mirena compared to Thermal Balloon[183], hysterectomy[184] and TCRE.[185;186]

Cooper at al randomised patients to either medical (oral) treatment or TCRE.[15] The study was pragmatic in design, methodologically sound and adequately powered. Follow up data at 4 months[15], 2 years[181] and 5 years[182] is available (the data from the five year follow-up will be presented later in this thesis) .

At 4 months women allocated transcervical resection were significantly more likely to be totally or generally satisfied, to find the treatment acceptable, and willing to have the treatment again. Pain and bleeding scores were significantly reduced by medical treatment but this reduction was modest in comparison with that seen after transcervical resection. Quality of life scores improved in both arms, although only transcervical resection returned them to normal values. The parallel partially randomised patient preference trial yielded some interesting data.[187] Overall, more women participated in the partially randomised patient preference design. There was no difference in the

numbers who agreed to be randomised. Women who expressed a treatment preference exhibited certain characteristics. Those wishing medical management tended to have better general health, to be less restricted by their menstrual problems, with fewer having been previously treated by their general practitioner. Those with a preference for transcervical resection of the endometrium had all tried medical management and had higher bleeding scores. Follow up satisfactions and acceptability rates, and Short Form 36 scores were highest after transcervical resection of the endometrium, whether chosen or randomised. Acceptability and a desire to continue the same treatment was greater among those who chose medical management than those randomly allocated it.

At two years women allocated medical treatment were significantly less likely to be totally or generally satisfied, to find their management acceptable or to recommend their allocated treatment. By two years 59% of the women in the medical arm had undergone TCRE, hysterectomy or both, whereas 17% in the TCRE cohort had undergone further surgery. Bleeding and pain scores were similar in the groups. A greater improvement in Short Form-36 health survey scores was seen in the TCRE arm. They concluded a policy of early TCRE to be effective, and does not result in an increase in hysterectomies at two years.

A small number of RCT exist comparing Mirena to surgical management.

Crosignani et al [186] randomised 70 women referred for hysterectomy in a 1:1 ratio to either insertion of a Mirena or TCRE in the early proliferative phase. Follow up was to a year. 65% of women using a Mirena reporting amenorrhoea or hypomenorrhoea at 1 year compared to 71% in the TCRE arm. Satisfaction was high for both procedures - 85% in the Mirena arm and 94% in the TCRE arm. Health Related Quality (SF 36) was not significantly different. . Whilst these figures are encouraging the generalisability of the results are significantly reduced by a number of factors. These factors are the small numbers, the invalidation of the power study, and the restriction of recruitment to women over 38 years who were referred for hysterectomy. These all reduce the ability to apply the findings to the general population. The use of PBLAC menstrual diaries in the recruitment and follow-up (see earlier comments on PBLAC) has its own problems.

1.3.3 Hysterectomy or Endometrial Ablation- Results and Safety.

When TCRE and ELA were introduced into the United Kingdom a number of randomised trials were carried out comparing these new techniques to hysterectomy.
As the complaint of DUB is rather subjective, and selection criteria for surgery vary it was essential to perform randomised controlled trials to compare endometrial ablation to hysterectomy.
Randomised controlled trials (RCT) have compared the procedures to hysterectomy. To date there are five RCT which have varied in methodological soundness.

The first, by Gannon et al [188], randomised 51 women on a waiting list for hysterectomy to either abdominal hysterectomy or TCRE (1:1 ratio). There was no power calculation or intention to treat analysis. The patients in the ablation group received oral progesterone as endometrial preparation. The patients were followed up to nine months.

The second trial by Dwyer et al randomised two hundred women to TCRE or abdominal hysterectomy [189]. A sample size calculation was made and the trial adequately powered. The uteri were not prepared pharmacologically. Patients were followed up clinically for 4 months in the initial report, and to two years in a follow-up paper by Sculpher at al [190]. The level of satisfaction recorded at 4 months for hysterectomy was 94% versus 85% for TCRE (just statistically higher). It also showed TCRE to have a significantly shorter hospital stay and a significantly faster time of return to work and daily activities. Economic analysis revealed TCRE as 53% of the cost of a hysterectomy (mean total costs) at 4 months, and 71% of the costs at an average follow-up of 2.2 years [190] .

The third trial by Pinion et al in Aberdeen randomised 204 women to hysterectomy or a conservative ablative technique (ELA or TCRE sub-randomised in a 1:1 ratio) [191]. The trial was adequately powered to detect a 20% difference in satisfaction between hysterectomy and ablation. The trial was not powered to detect a difference in satisfaction between the two ablative techniques although the results were very similar.

At twelve months, 89% in the hysterectomy group and 78% in the conservative surgery group recorded themselves as very satisfied with the results of their procedure. Significantly less early morbidity, faster operative times and shorter post-operative stays were recorded by the conservative groups. The 5 year follow-up revealed 76% of the conservative group avoiding hysterectomy. [192]

The multi-centre RCT Medical Research Council trial reported by O'Connor et al, randomised 202 women to TCRE or hysterectomy in a 2:1 basis. [193] Primary end points were women's satisfaction and the numbers requiring subsequent surgery. The trial was powered to detect up to a 15% difference in the proportions of women dissatisfied with their treatment at three years. The multi-centre (9 UK centres) nature of the trial enhances the ability to generalise the results, however, of the approximately 800 eligible patients, approximately 600 refused randomisation. Endometrial preparation prior to TCRE was at the discretion of the operator. At a median follow-up of 2 years, 96% in the hysterectomy group and 85% in the TCRE group recorded satisfaction with their results (statistically non-significant). Further surgery was seen in 22% of the TCRE arm at 3 year follow-up and 9% in the hysterectomy arm. The prolonged recruitment time, low number of eligible women recruited (this may be an effect of private practice), and the fact that the hysterectomy findings are based on the 28 women in the hysterectomy group affecting the trials external validity.

The fifth trial was a randomised comparison of endometrial resection (TCRE) with vaginal hysterectomy (VH). [194] Some may argue that the comparison with vaginal hysterectomy is a more valid comparison than the comparison to abdominal hysterectomy. The preferred route for hysterectomy of a normal sized uterus with associated dysfunctional uterine bleeding is vaginal. The vaginal route with its associated lower morbidity, shorter hospital stay and faster recovery would be a more valid comparison to ablation

The study by Crosignani in Milan recruited menorrhagic women, less than 50 years, with uteri 12 week size or less. [194] 85 women were randomised (44 VH / 41 TCRE). They assessed satisfaction at two years (very satisfied or satisfied) in the 77 followed up. 87% of the resection arm and 95% of the hysterectomy arm reported satisfaction. Quality of life scores, social functioning and vitality scores were significantly higher for hysterectomy and anxiety and depression scores were significantly lower. There were no significant differences in sexual function (Sabbatsberg Sexual Rating Score) and improvements were seen in both groups.

These Randomised Control Trials established the validity of the ablative procedures, securing its evidence base and legitimising many of the claims made in earlier non-randomised observational studies. The studies, whilst differing in methodology, shared many common features. The uteri were all 10 – 12 week size and the procedures performed to similar techniques. The similarity in outcome is striking, with TCRE / ELA recording comparable (although lower) levels of satisfaction to hysterectomy (hysterectomy however, never achieving 100%). The common finding of shorter operating times, rapid recovery, lower morbidity and faster return to normal activity is noticeable. The ability of ablative techniques to reduce dysmenorrhoea and pre-menstrual symptoms was noted as was the improvement, where measured, in the quality of life and psychological scores. The rates of further surgery were similar.

Importantly these studies were pragmatic in design and included women with uterine enlargement up to the size of a 10 or 12 week pregnancy. Twenty percent had fibroids identifiable at hysteroscopy. In Pinions study (hysterectomy group) endometriosis was found in 8% and adenomyosis in 17% of the women so it can be assumed that the women in the TCRE group contained had similar pathology. This meant that the women in these studies were not carefully selected to only include women with no pathology and regular uterine cavities.[195]

Long term follow up of the Pinion study from Aberdeen has been published [192]. The follow up period was a median of 5.1 years (range 4 – 6 years). Hysterectomy was

avoided in 76% of the hysteroscopic surgery group. There was no significant difference between the two groups as 89% of patients were totally or generally satisfied after hysterectomy and 80% after hysteroscopic surgery. Life table analysis showed that hysterectomy was only seldom needed once women were beyond 36 months after their hysteroscopic surgery. This result is reassuring as it shows that in this group of women hysterectomy was avoided in three-quarters of them. This is despite the fact that these women were expecting a hysterectomy and its associated amenorrhoea. In the hysterectomy group 7% were dissatisfied with the results of the procedure compared to 9% in the hysteroscopic surgery group showing that satisfaction is not universal following hysterectomy for DUB.

Persistence of pelvic pain following endometrial ablation is a common reason for apparent failure of the technique and the cause for a subsequent hysterectomy. In that study 15% of women continued to suffer from pelvic pain four to six years after hysterectomy compared to 18% after hysteroscopic surgery. If abdominal or pelvic pain continues following endometrial ablation pain it is investigated and managed, often by hysterectomy, whilst after hysterectomy it is either ignored or thought to be not a gynaecological problem.

The above study also gave some evidence as to the relative effects of hysterectomy and endometrial ablation on sexual function. Both groups reported either no change or an improvement in sexual interest and satisfaction.

Further work was done on this study population to compare the psychological effects of hysterectomy and hysteroscopic surgery. There was a similar beneficial effect on anxiety, depression and sexual function between both groups at six and twelve month's post operatively. When re-assessed between four and six years post operatively there was no difference between the groups. The improvement over the pre-treatment score in the Hospital Anxiety and Depression Scale for both anxiety and depression were maintained [192;195].

McPherson et al reported on the effect on psychosexual health of ablation and hysterectomy at five years.[196] They compared three groups TCRE, hysterectomy (sub-

total and total) with oophorectomy and hysterectomy (sub- total and total) without oophorectomy. The groups were comparable except the oophorectomised group was older. They looked at self reported psychosexual health in a unselected population of 11,325 women based on groups derived from the MISTLETOE[173] and VALUE[197] studies. They asked to rank how much they were bothered with regards to their loss of interest in sex, difficulties in becoming sexually excited and vaginal dryness using a four point Likert Scale. They revealed (adjusting for age and HRT) that crude and adjusted prevalence of psychosexual problems was higher after hysterectomy than TCRE especially if accompanied by bilateral oopherectomy.

In a similar fashion to the psychosexual health study, and using the same cohorts of TCRE, hysterectomy and hysterectomy with oopherectomy McPherson reported a separate paper on self reported bladder symptoms at five years derived from the MISTLETOE and VALUE studies populations. [198] The findings were that the odds of severe urinary incontinence, urinary frequency and nocturia were increased with hysterectomy.

The relative symptomatic results of the two treatment approaches are best assessed by the use of randomised controlled trials as shown above. These are large enough to give an indication of the relative frequency of common complications, but for the study of uncommon complications large prospective series are needed. Fortunately two such audits of the hysteroscopic methods have been carried out in the U.K. and recently (and perhaps belatedly) one on the complications of hysterectomy.

1.3.4 Complications of Endometrial Resection and Ablation

The introduction of these new surgical techniques elicited concerns over safety. The move from the dedicated proponents into the hands of the generalist is a delicate one. Initial high success rates and low complication rates may be misleading. Over time new complications became evident. Cases of uterine perforation, cervical laceration, false

passage creation, haemorrhage, sepsis and bowel injury were reported. Complications of fluid overload, seen previously by the Urologists in Post Transurethral Resection of the Prostate Syndrome (Post TURP Syndrome), were reported. The use of 1.5% Urological Glycine (non ionic) irrigation fluid in TCRE and RBEA was reported to be associated with serious and occasionally fatal consequences. This fluid is non-miscible with blood (hence improving vision) and non-ionic (allowing intrauterine electrosurgery). However the potential to cause significant hyponatraemia if absorbed (via open uterine vessels or transperitoneally) was present. The resulting hyponatraemia caused cerebral oedema (confusion, agitation, coma), pulmonary oedema and metabolic acidosis from ammonia metabolites. Cases of death from respiratory arrest with compression of the respiratory centres due to cerebral tonsillar herniation were reported [199;200]. Current recommendations limit total fluid absorption to 1500 mls, with the advice to abandon the procedure if this limit is exceeded.

Whilst minor complications such as post operative endometritis, prolonged bleeding and transient pelvic pain are relatively common, more major, potentially life threatening complications do occur, albeit infrequently. Transient bacteraemia has been shown to be relatively common post ablation with low grade endometritis being seen in approximately 1% of cases [201], and a death secondary to overwhelming sepsis has been reported [202]. Antibiotic prophylaxis is recommended by many as good practice although its does not have a solid evidence basis [203].

Post–tubal sterilisation syndrome [204-206] is a late complication associated with endometrial ablations. This occurs when cervical stenosis prevents menstrual loss draining transcervically and tubal sterilisation prevents retrograde menstruation. The resulting haematometra causes dilation of the proximal portion of the fallopian tube resulting in a history of post ablation cyclical pelvic pain, occasionally an adnexal mass, raised CA 125 and tenderness. Many mimic ovarian pathologies such as ovarian cancer

or cyst accidents. Ruptures have been reported. Previous sterilisation is an independent risk factor for hysterectomy [207;208].

Pregnancies have been reported following ablation. Many advise offering women sterilisation as a permanent method of contraception at the time of ablation, with significant numbers already using female or male sterilisation prior to ablation. The concerns over the safety for the mother and the pregnancy are significant. The risks are miscarriage, preterm labour, intrauterine growth retardation, placental implantation abnormalities (placenta accreta, increta, percreta) and abruption. Occasional normal outcomes have been recorded but such are the concerns over the risks to the mother and unborn child that therapeutic abortion is to be recommended. Up to June 2002, Cook et al reviewed the reported pregnancies post ablation [209]. They reported only 17 pregnancies progressing beyond 20 weeks and a single successful term pregnancy.

The incidence of complications following the hysteroscopic methods of TCRE and ELA has been determined firstly by the Scottish Audit of Hysteroscopic Surgery [210] then by the MISTLETOE study in England and Wales [173] which between them give the results from over 11 000 patients. In both audits it was estimated that over 90% of procedures were reported and that there was no difference in the complication rate in the unreported group. In the MISTLETOE study of over 10 000 cases the rate of bowel damage due to TCRE was 0.7/1000 [173]. The Scottish Audit of Hysteroscopy Surgery of just under 1,000 cases reported no cases of bowel damage. One case which was reported to the audit as a uterine perforation and laparoscopy following TCRE, was actually a case of small bowel damage. The patient subsequently required a laparotomy after the registration form was returned. This gives a rate of 1/1000 for bowel damage due to TCRE. Endometrial Laser Ablation (ELA) is felt to be safer than TCRE with no case of bowel damage in 1764 cases in MISTLETOE and 314 in the Scottish Audit but there was a case of small bowel damage in the Aberdeen randomised study [191].

Rollerball endometrial ablation (RBEA) is a first generation method derived from TCRE and felt to be a safer method as the surface of the uterine cavity is coagulated rather than resected. No visceral damage was reported with this method in MISTLETOE, but there were only 650 cases [173]. There have been a number of case reports of large and small bowel damage after REA [211;212]. In the MISTLETOE study the rate of emergency hysterectomy was 6/1000 overall, but 11/1000 when TCRE was performed using a loop for the whole procedure. In the Scottish audit the emergency hysterectomy rate was 2/1000, considerably lower than the English audit. Uterine perforation is reported in 15/1000 cases in the MISTELTOE and 10/1000 in the Scottish audit [173;210]. This is of little consequence if the perforation is recognised and does not involve the use of electro-diathermy or laser energy.

As all the hysteroscopic methods use fluid to distend and irrigate the uterine cavity, excessive absorption of irrigation fluid is a potential risk. During TCRE using Glycine, changes in electrolytes especially serum sodium can be avoided if the procedure is abandoned when absorption is noted to be reaching 1500ml. In MISTLETOE there was a 1% rate of fluid absorption of greater than 2000ml and 1% in the Scottish Audit. Both audits and a RCT comparing TCRE to ELA have shown a greater rate of fluid absorption following ELA as compared to TCRE [173;210;213]. The increased fluid absorption post ELA however is not as much of a concern as that seen with TCRE as saline is used with ELA. Combining the two audit studies the mortality from the hysteroscopic methods of endometrial resection and ablation was 0.27/1000 [173;210].

In conclusion the two studies reported on over 11,000 cases. ELA and RBEA were revealed as the safest techniques (albeit with a smaller number of procedures performed), with higher rates of perforation and emergency hysterectomy seen in the TCRE cases.

1.3.5 Complications of Hysterectomy

The complications of hysterectomy are often underestimated. Minor pyrexial morbidity was found in 47% of women after abdominal hysterectomy in the Pinion study with 11% having a vaginal vault haematoma and 5% requiring a blood transfusion [191]. There were also three major complications in that series.

The VALUE study in England , Wales and Northern Ireland is the most recent assessment of complications[197]. Unfortunately, unlike its sister publication the MISTLETOE study, the numbers included were a minority of the total number of procedures and there is a strong suspicion of a general under reporting of cases and their complications.

The Value study assessed serious operative and post-operative complications (to six weeks) of hysterectomy in a prospective cohort of women undergoing hysterectomies for benign indications. A total of 37,512 women from 276 NHS and 145 private hospitals were studied. This group was originally recruited to compare the outcomes of endometrial destruction with those of hysterectomy. Severe operative complications occurred in 3%. The risk decreased with age and increased with greater parity and history of serious illness. Women with symptomatic fibroids experienced more complications than women with dysfunctional uterine bleeding [adjusted odds ratio = 1.3, (95% CI 1.1-1.6)]. Laparoscopic procedures doubled the risk of operative complications of abdominal hysterectomy [adjusted odds ratio = 1.9, 95% CI 1.5-2.5)]. Post-operative complications occurred in around 1% of women, with a slight decrease with increasing age, and the strongest risk factor was a history of operative complications. Hysterectomies by the vaginal and laparoscopic route had significantly higher adjusted risks than abdominal operations (0.9%), RR = 1.4 (95% CI 1.0-1.9) and RR = 1.6 (95% CI 1.0-2.7).No intra- operative deaths were recorded. 14 women died within the six-week post surgery giving a crude mortality rate of 3.8/1000, (range 2.5-6.4).

There is a large retrospective study from the United States of 1851 pre-menopausal women undergoing hysterectomy.[214] The hysterectomy were performed by the abdominal route in 1283 and vaginally in 568 women. The rate of fever after abdominal hysterectomy was 30% and 15% needed a blood transfusion. Vaginal hysterectomy had a lower rate of febrile morbidity of 15%. Bowel injury occurred in 3/1000 women following abdominal hysterectomy and 6/1000 after vaginal hysterectomy. The urinary tract was damaged in 3/1000 after abdominal hysterectomy but 14/1000 with the vaginal route. The mortality was 1/1000. A similar rate of bowel damage has been found in another large American study where the rate of bowel damage in abdominal gynaecological surgery has been reported as 8.4/1000 and 7.3/1000 for vaginal surgery [14]. Though the Dicker study advocated vaginal hysterectomy because of a 70% higher rate of complications after abdominal hysterectomy the difference was mainly caused by relatively minor febrile problems. There was however more damage to the bowel or urinary tract during vaginal hysterectomy [13].

1.3.6 Patient Selection for Ablation

Whilst some selection criteria are fairly obvious, others have become clearer as the evidence has accrued. From the beginning the ablative procedures have only been offered to women whose family is complete because of the probable sub-fertility and the potential risks to both to mother and foetus of a pregnancy following endometrial ablation. As it became obvious that pregnancies could occur after ablation, women had to continue adequate contraception after the procedure.

It was also obvious that ablation would not deal with a very large fibroid uterus.

There is now evidence as to the prognostic factors for successful ablation based on randomised trials and the large audit studies. Women whose menstrual blood loss is genuinely excessive have a better outcome after TCRE than those with normal menstrual

blood loss. Gannon showed that if menstrual blood loss was above 80 ml per cycle the subjective failure rate was 9% compared to 18% if periods were perceived to be heavy but who had normal menstrual loss.[19] Patient age may be important with younger women having a lower satisfaction than older women. Studies in different medical fields and interventions have shown that expression of satisfaction is affected with age, with older people in general expressing higher levels of satisfaction.[215] The Scottish Audit of Hysteroscopic Surgery showed a lower satisfaction in women less than 40 years of age, though this was still 79% as compared to 88% in women aged more than 40. [210]

The presence of irregular periods or menstrual dysmenorrhoea is not a predictor of a poor outcome. In the trial comparing TCRE and ELA there was no difference in satisfaction using either of these criteria. [213]

Whether endometrial ablation of the endometrium succeeds or fails is probably dependant on a number of variables, with genuine and perceived severity of symptoms, patient expectation and uterine pathology all playing their part. In addition there is the individual variation in efficacy and performance of the procedure as well as the pathological healing processes in the uterus.

One method of determining reasons for the failure of endometrial ablation is to look at the pathology of the uterus in women who have a hysterectomy for failure. The draw back is that it tells us nothing about the women who have had a successful ablation.

Davis et al have studied the histopathological status of the removed uterus following hysterectomy for failure of REA to control symptoms. [216]. In women still complaining of bleeding excessively they found that endometrium was present focally but not diffusely in the uterine cavity. Fibroids were found in 30% and adenomyosis in 27%. As already stated in the Pinion study, where the women had a clinical diagnosis of dysfunctional uterine bleeding, those randomised to hysterectomy were found to have endometriosis in 8 %, adenomyosis in 17 % and fibroids in 20%. [191] Presumably as it was a randomised study the same uterine pathology would be present in those women undergoing TCRE or ELA. Despite this the hysterectomy rate 4-6 years after treatment is only 22%. It is probable that even in women with this range of pathology, many will

have a satisfactory result from endometrial ablation if the indication for endometrial ablation is DUB rather than pain.

1.3.7 Which Method of Endometrial Ablation

1.3.7.1 First Generation Techniques

A large number uncontrolled series of TCRE and ELA have been published as well as randomised studies comparing them to each other and to medical treatment. The two uncontrolled studies that give the best estimate as to the long-term outcome are the long term follow up of TCRE from the Magos group[217] and ELA from Garry's group[218]. Magos followed up 525 women for up to five years. Despite the apparent long term nature of this study the mean follow up was actually 31 months and only 43 women were followed up for the full five years. The hysterectomy rate was only 9% and 80% avoided further surgery. The Middlesbrough group (Garry) have reported long term follow up of 1000 ELA procedures, with 746 women followed up for up to 6 years. The rate of repeat surgery was 15% during the period of follow up, but by using life table analysis they predicted a hysterectomy rate of 21% at 6.5. years.[218] Despite the size of these studies they are less useful than the long term follow up of randomised controlled trials because the duration of follow up is not uniform for all women in these studies. They therefore rely on statistical estimation of the final hysterectomy rate. The other drawback is the fact that in an uncontrolled series the degree of symptomatology of these women at the start of treatment is unknown. These studies along with long-term follow up of the Aberdeen randomised trial show that the great majority of women will avoid a hysterectomy following first generation endometrial ablation.

TCRE has been compared to ELA in a randomised trial of 372 patients. This study showed that TCRE had a shorter operating time than ELA. There was less mean fluid absorption following TCRE and fewer patients had large volume absorption during TCRE than with ELA. Clinically this difference is irrelevant as ELA utilises normal saline and therefore doesn't pose the same risks as the glycine utilised in TCRE. There were no differences in complications between the two methods and the only major complication was a case of small bowel damage after ELA. There was no difference in outcome as measured by satisfaction (90%), amenorrhoea rate (45%), or hysterectomy rate (20%) between the two methods [213].

Rollerball Endometrial Ablation (REA) is a widely used method especially outside the United Kingdom. Uncontrolled results give this method a similar success rate to the other hysteroscopic methods [219].

1.3.7.2 Second Generation Techniques

Second generation ablative techniques represent a rapidly expanding area of medical technology. The majority use tissue heating as the method of endometrial destruction using electrical energy (Vesta System – multielectrode), microwave energy (Microwave Endometrial Ablation), laser (ELITT), heated saline / glycine irrigating the uterus (Hydrotherm Ablator and Circulating Hot Saline) or heated saline / dextrose contained within a balloon device (Thermachoice and Cavatherm Systems). Second generation techniques are mostly blind in nature (no hysteroscopy), and most avoid the need for fluid distension media and its risks. They are quicker and much simpler to learn and perform than first generation techniques, which many gynaecologists found difficult or impossible to master. Some also offer the benefits of local anaesthesia (Microwave Endometrial Ablation and Thermachoice).

These new procedures all post date the earlier national safety audits [173;210]. The new techniques must prove equal efficacy but also safety before they can become widely accepted. Their efficacy should be compared in randomised trials of adequate power to

the now established gold standard of TCRE. Adequate training is vital to reduce the potential for serious complications with the second generation techniques.

The methods which have been subject to adequate assessment to date are Thermachoice (Gynaecare UK Ltd) [210;219-221], Microwave Endometrial Ablation (MEA – Microsulis UK Ltd) [222;223], Vesta system [224], Novasure device (Novacept Inc) [225], Heroption (Cryogen Inc) [226] and the Hydrothermablator (Boston Scientific Corp) [227].

1.3.7.3 Thermal Balloon Therapy

Thermal balloon therapy has been compared in an RCT to Rollerball Ablation (RBEA) which, although a first generation technique, has not been validated against hysterectomy or TCRE and as such is therefore not seen as a gold standard.

Thermachoice Thermal Balloon utilises a 16 cm long, 3.1 mm diameter catheter. Three cables link the device to the control unit. One is the electrical connection, the second the fluid line and the third supplies the impeller. The distensible silicone balloon is filled with 5% dextrose solution at a working temperature of 87 degrees Celsius and a distending wall pressure of 160 -180 mmHg. Treatments are completed in 8 minutes. A predictable 5mm endometrial thermal destruction is achieved when utilising these parameters.

Thermachoice III, the currently marketed version, contains an impeller which circulates the dextrose solution to ensure an even thermal effect (previous models were troubled by uneven heating). The technique is blind and after sounding of the cavity dilatation is rarely required. The device requires a minimum of 150 mmHg pressure before the heating element is activated. Failure to maintain this pressure will result in an automatic cut of if pressures exceed 200mmHg or less than 45mmHg. Prior to treatment the catheter requires priming with 5% dextrose to establish the balloon is intact and it is then inserted into the cavity and filled with between 10 mls and 30 mls of dextrose to stabilise the pressure at 160 -180 mmHg. Extra dextrose can be introduced during

treatment if a small pressure fall (as a result of uterine relaxation) is encountered, a larger drop however should raise concerns of a leaking balloon or a uterine wall defect.

A multicentre North American trial randomised 275 women to thermal uterine balloon therapy (Thermachoice) or RBEA to study efficacy and safety [221]. The study was powered to detect 20% lower efficacy for RBEA versus balloon. The study was restricted to women with small, regular uterine cavities and with high PBLAC scores and therefore the results are less generalisable to an unselected population than the trials of first generation methods. No pre-treatment endometrial hormonal preparation was used in either arm, instead the endometrium was prepared with a five minute suction aspiration. At 1 year both techniques significantly reduced the PBLAC score, 68.4% in the RBEA arm and 61.6% in the Balloon arm had a reduction of over 90% from their pre-operative baselines scores. This difference was not significant. Quality of life scores, satisfaction and improvement in dysmenorrhoea / PMS were also similar. The balloon treatment was significantly quicker with no complications, compared to a complication rate of 3.2% of the RBEA group. The amenorrhoea rate was significantly lower after Thermachoice (15%) compared to (27%) after RBEA, despite the fact the amenorrhoea rate after RBEA was considerably less than expected with a first generation method. This study was re analysed at 2, 3 and 5 years of follow up [219;220;228]. At two years follow up it was found that in total 15 hysterectomies had been performed, 11 in the RBEA arm and 4 in the balloon arm. Of the 214 who were followed for 3 years, the results of uterine balloon therapy and Rollerball Endometrial ablation remained similar, with little difference at 3 years compared with results at 1 year. There was a suggestion of an increase in hysterectomies in the RBEA group (n=14) compared with the uterine balloon therapy group (n=8) at 3 years [220].

The conclusion was that both methods were highly successful at avoiding hysterectomy and relieving symptoms and that patient satisfaction remained high.

A European RCT by van Zon-Rabelink et al [229] from Holland recorded similar results to Loffer in their 2 year study of women randomised to Thermachoice or Rollerball.

Thermachoice was significantly more successful at reducing menstrual blood loss with equivalent success rates (as defined by a PBLAC scores) measured at 24 months post-operatively. Satisfaction rates were not significantly different (respective 75% for roller ball and 80% for uterine balloon).

Data regarding the use of Thermachoice III in an outpatient setting has been published. [230] In a prospective observational study trained non-specialists (General Practitioners) performed outpatient treatments in a community hospital under the indirect supervision of a consultant gynaecologist. Patients were screened with a normal endometrial biopsy, cavity length and ultrasound by a radiologist with a special interest in gynaecological transvaginal ultrasound scan. Of the 166 referred 87 women treated. There were no complications and all procedures were well tolerated. They commented on the suitability of the technique as an outpatient technique possibly even as a procedure for primary care. The findings are interesting. Its validity is affected by the high numbers found unsuitable (n = 79, nearly 50%) and the highly selected group who were operated on. Also the subjects were not randomised and bias will have entered the selection of cases. There are the wider issues of performing the procedures without direct specialist input.

A randomised comparison with the second generation ablative technique of the Thermal Balloon is published. [183] The study was based on 50 women in a district general hospital who were randomised to either surgical treatment using thermal ablation (Thermachoice) or medical treatment using a LNG-IUS. PBLAC diaries were used at recruitment and 6 month post procedure. Follow-up was possible in 23 women in the Thermachoice group and 21 women in the Mirena group. Median post-insertion /operative menstrual scores were 27 for the Thermachoice group and 19 for the Mirena group ((P=0.689). It is notable that at entry the median menstrual scores were higher in the Thermachoice arm. The study concluded that both Thermachoice endometrial ablation and a Mirena LNG-IUS are equally effective in the management of menorrhagia and treatment choices should be tailored to the woman's needs and preferences. The small numbers, short term follow-up and lack of a power study limit the interpretation of these results

Cavatherm a thermal balloon endometrial ablation device is similar to Thermachoice in that it utilises a heated dextrose solution filled silicone balloon. Similarly it uses an impeller to circulate the heated solution and takes 10 minutes to complete therapy. The main difference is that the Cavatherm balloon has an adjustable balloon length to allow treatment of cavities from 5 to 10 cm in length.

Cavatherm has been compared to the gold standard of TCRE. Pellicano et al have reported an Italian RCT of Cavatherm versus TCRE with 2 years follow up.[231] 82 patients were randomised in a 1:1 ratio to TCRE or Cavatherm with patient satisfaction as the main outcome measure. All women had failed medical treatment with uteri less than 12 weeks gestation in size. There were 23 post randomisation, pre-treatment drop outs. The inclusion criteria were restrictive with all women undergoing a hysteroscopy, TVUSS and haematological work up. The TCRE arm was pre-treated with GNRH analogues whilst those in the Cavatherm arm were not. All procedures were undertaken under spinal anaesthesia. Follow up to two years was achieved in 75.3% in the TCRE arm and 87.5% of the Cavatherm arm. The satisfaction rate was significantly higher in the thermal destruction group. Operative time was significantly shorter in the thermal destruction group. Intra-operative blood loss was significantly lower in the thermal destruction group. Re-intervention rates were higher in the transcervical hysteroscopic endometrial resection group at two years (15.1% vs. 5.7%). Discharge time, complication rate, and resumption of normal activity were not significantly different between the two groups. They concluded that Cavatherm thermal destruction of the endometrium for the treatment of menorrhagia should be considered an effective therapeutic option.

1.3.7.4 Microwave Endometrial Ablation

This will be discussed fully in Section 1.4.

1.3.7.5 Multi-electrode Systems

The Vesta System – a disposable distensible multi-electrode carrying balloon utilising mono-polar diathermy has been compared in an RCT to combined resection / coagulation technique (TCRE). Women with menorrhagia as defined by PBLAC scoring (>150), with normal cavities and who had failed medical treatment were randomised.[224] Out of the 557 women assessed as menorrhagic only 244 were randomised, as approximately half proved unsuitable for the procedure by the other inclusion parameters. PBLAC's were used in selection and definition of outcome success (a score PBLAC < 75 defined success). Success was achieved in 86.9% of the Vesta arm and 83% in TCRE at one year. Amenorrhoea rates were 31% in the Vesta arm and 34% in the TCRE arm. No significant complications were reported. 87% of the Vesta procedures were performed on an outpatient basis, under local anaesthesia +/- sedation. Of note there were 18 (10.6%) technical failures in the Vesta arm and one Vesta procedure had to be abandoned as the device had entered a weakened caesarean scar. The benefits of avoiding fluid overload and local anaesthesia were present. The allocation of the procedure to local anaesthesia was at patient and physicians discretion and thus as a non randomised outcome the findings lack generalisabilty. They concluded the Vesta method to be equally effective and safe as TCRE. The Vesta system is however not currently being commercially marketed.

1.3.7.6 Hydro Thermablator Procedure

Hydro-thermablator, unlike the rest of the second generation techniques, requires hysteroscopy and gives a view of the cavity during active treatment. No manipulation of the device once placed in the uterine cavity is required. The technique relies upon

circulating heated saline within the endometrial cavity. The saline is heated externally prior to being introduced into the hysteroscope and achieves an intrauterine temperature of 90 degrees Celsius. The fluid is constantly re-circulated at a rate of 300 mls / min. This method is suitable for cavity lengths from 4 cm and for irregular and fibroid cavities unlike the balloon methods. Intrauterine temperature can be maintained with cavities up to a volume of 60 ml although this size of cavity is unlikely to be selected for ablation (10 - 30 ml is the average). The device is 7.8mm in diameter and takes 10 minutes of active treatment, with a post treatment cool down of 1 minute prior to device removal. A pre-treatment test run using saline at room temperature is carried out to ensure the circuit is intact; a loss of only 10 mls from the system will trigger an automatic shut down. The intrauterine pressure is maintained at a net pressure of 50 – 55 mm Hg, thus preventing spillage from the fallopian tubes which is only apparent at 70mm Hg or above [232;233]. An adequate seal at the cervix is imperative and care must be taken not to over dilate the cervix. The pressure is maintained by the balance between the hydrostatic mechanism and the pump evacuating the saline from the cavity. The saline is suspended from a dedicated intravenous pole 115 cm above the patient's uterus. The main advantages of the technique are the pre-operative hysteroscopic view of the cavity (to exclude false passage / perforation formation) with saline at room temperature the fact that the device can accommodate any hysteroscope up to 3mm or smaller, and the ability of the technique to treat irregular cavities. A pharmacological endometrial preparation is essential which is expensive, cause side effects and increases cervical resistance.

A multi-centre RCT study comparing Hydro ThermAblator (HTA) to Rollerball (RBEA) is published. [234] Nine centres in North America were included. The trial was part of a Food and Drug Administration Phase III clinical trial seeking approval for the device in the United States. 276 patients with menorrhagia were randomised using computer generated randomised blocks, in a two to one ratio, to HTA (n = 187) or Rollerball (n = 89). PBLAC diaries were used for inclusion criteria and follow-up. Women between 30 and 50 years were included. Uterine cavities between 4 and 10.5cm were included. The inclusion of irregular cavities is of note for this second-generation technique. Intramural

fibroids / polyps less than 4 cms, sub-mucous fibroids and anatomical variants up to partial sub-septated were included. Success was defined as a PBLAC score of < 75. Success rates as defined were 77% after HTA and 82% for RBEA. Amenorrhoea rates were 40% after HTA and 51% after RBEA at one year (percentages were of the evaluable population). They concluded that HTA was safe and effective; it offers safety benefits with the associated use of hysteroscopy and the potential to be performed as an outpatient procedure. As with many new technologies technical problems may arise, and seven HTA procedures were only partially completed secondary to technical failures.

Medium term data on the multicentre Hydro Thermablator Trial (3 year) have recently been published. [235] 276 women were randomised to HTA or RBEA. The amenorrhoea rate at three years was 53% in the HTA group and 46% in the RBEA group. Reduction to normal bleeding or less was reported by 94% in the HTA group and 91% in the RBEA group. Patient satisfaction was reported by 98% in the HTA group and 97% in the RBEA group. 16 (9%) in the HTA group and 5 (6%) in the REA group required hysterectomy. Repeat ablation was performed in 3 (2%) of the HTA and 3 (4%) of the RBEA. A conclusion of equivalent efficacy between HTA and RBEA was made. Although not a primary outcome measure, 45% of the HTA procedures were performed under local anaesthesia +/- sedation. These claims, whilst encouraging, do not support a conclusion in an unselected population. The initial safety problems with 2 external burns to leg / buttock in the HTA group were an initial, now rectified, design fault, with burns secondary to contact with the then un-insulated hot saline tubing in anaesthetised patients. Worldwide, over 10,000 HTA treatments have been reported to date.

1.3.7.7 Novasure Procedure

Novasure is a second generation device that utilises a conformable, three dimensional bipolar gold plated mesh mounted on an expandable frame to deliver bipolar energy to the cavity [236]. The device has a disposable hand held instrument 7.2 mm in diameter that

is suitable for cavities up to 12 cm in length. The instrument incorporates an intra-cornual measuring device retracted into a protective sheath that allows the uterine cavity width to be measured. An adjustable sheath accommodates and protects the cervix during active treatment preventing endo-cervical burns that can lead to haematometra formation. Energy delivery is regulated by two factors, firstly the cavity length and width measurements that are input to the control unit by the operator, and secondly by the measurement of tissue impedance. The progressive vaporisation and desiccation of the tissues caused by the electrical energy increases tissue impedance as tissue water content diminishes. The endometrium is vaporised and evacuated by the constant suction applied to the cavity during the procedure. The myometrium desiccates and once the tissue impedance reaches 50 Ohms the device automatically terminates the procedure. This tissue impedance factor allows the device to be used on unprepared uteri and even during active menstruation by regulating energy delivery, only terminating treatment once the tissue impedance reaches the set 50 Ohms that represents adequate treatment. Average active treatment times are 90 seconds, representing the fastest second generation technique. The suction applied to the cavity is constantly maintained removing endometrial ablation by-products and ensures the endometrial tissue is well applied to the bipolar mesh. Perforation and inadvertent energy delivery to pelvic / abdominal contents is always a concern with blind techniques and as part of its process prior to activation the device has a cavity integrity assessment feature. This feature utilises carbon dioxide to insufflate the cavity to a set pressure (50 mm Hg), cavity integrity is confirmed if the pressure is maintained for 4 seconds. A poor seal around the uterine cervix may causes a leakage of carbon dioxide and false positive cavity integrity check such that the machine cannot be activated. Neither pre-operative pharmacological preparation nor immediate pre-operative hysteroscopy are required.

The Novasure device has been compared in a randomised control trial to hysteroscopic wire loop resection plus rollerball with follow up to one year [225]. Nine centres were included in this multi-centre international trial. 265 pre-menopausal women (age 25 – 50

yrs) were randomised in a 2:1 ratio to Novasure or hysteroscopic surgery. The procedures were performed on unprepared uteri at any time in the menstrual cycle. Inclusion was based on PBLAC scores > 150, regular cavity sizes 6 - 10 cm. Sub mucous fibroids / polyps < 2cm that did not obstruct the cavity were included. In the control arm the endometrium was prepared for rollerball ablation by prior loop resection. No preparation was used in the Novasure arm. The trial was a phase III trial as part of a submission to the United States Food and Drug Administration. The trial was funded by the manufacturer and the possibility for bias must be borne in mind. On the plus side the trial was multi-centre.

The amenorrhoea rate for Novasure treated patients was 41% versus 35% for the hysteroscopic arm, success as defined as a PBLAC score less than or equal to 75 (eumenorrhoea) was seen in 88.3% and 81.7% respectively. Mean procedure times for Novasure were 4.2 minutes versus 24.2 minutes in the hysteroscopic group ($p < 0.0001$). No perforation was seen in the Novasure group whilst three were reported in the hysteroscopic arm. Although not a primary or secondary outcome measure, anaesthetic use (left to individual clinicians / patient preference) was recorded. 73% of the Novasure procedures were performed under local anaesthesia +/ - sedation versus 18% under hysteroscopic surgery.

1.3.7.8 Cryosurgical Techniques

Cryosrgical techniques have been developed. Her Option, the endometrial ablative technique that utilises cryosurgical endometrial ablation to produce the desired effect on the endo/myometrium. The device uses a mixed gas coolant to generate temperatures of –90 to –100 degrees Celsius. Irreversible tissue death is seen at temperature below - 20 degrees Celsius. The device utilises a 5.5 mm probe that incorporates an electric heater, a thermocouple and a saline flush port. Intra-operative ultrasound is required. Treatment

is monitored with ultrasound that reveals the extent of ice ball formation and by the thermocouple display. The leading edge of the ice front corresponds to –1 to –2 degrees Celsius and the ultrasound image corresponds to within 1 mm of the actual depth of the cryo-lesion [237]. Instillation of 3 - 400 mls of warm saline into the bladder facilitates ultrasound scanning. The probe is inserted in to the cavity, its fundal position confirmed by ultrasound, and 5 mls of saline is instilled into the cavity to couple the probe to the endometrial tissues. Treatment begins with the probe angled to the first cornue to be treated. On average three ice balls are required, with the probe tip thawed (via the electric heater) to allow disengagement and repositioning of the device.

Work on extirpated and pre-hysterectomy uteri confirmed ice balls seen in the range of 24 – 34 mm in the first cornue treated to 28 – 37 mm in the second, and a depth of tissue necrosis of 9 - 12mm [238], the largest range reported by any device. This is greater than the 6 mm required to incorporate the basal layer of the endometrium and of slight concern as the thinnest cornual region may be only 7mm in thickness.

A randomised control trial of Her Option cryoabaltion versus rollerball ablation has been reported. The trial was multi-centre with 279 women recruited and randomised in a 2:1 ratio to Her Option or Rollerball. Pre-recruitment PBLAC and FSH of less than 40 iu/l were part of the inclusion criteria. Anaesthesia was at the discretion of the clinician / patient. Success, defined as a PBLAC score less than 75 (corresponding to eumenorrhoea), was seen in 77.3% after cryoablation and 83.8% after rollerball. 92% of cryoablations were performed under local anaesthesia versus 46% of rollerballs. The use of a freezing effect rather than a thermal effect as used in the other treatment options is seen as the reason behind the large number of procedures being performed without general anaesthesia, although acceptability of anaesthesia was not a randomised outcome measure.

1.3.7.9 Photodynamic Therapy

The use of photosensitising drugs delivered to the endometrium and then used to destroy the sensitised tissue has been described.

5-Aminolevulinic acid (ALA) when added to many tissues, results in the accumulation of sufficient quantities of the endogenous photosensitizer protoporphyrin IX (PpIX). When exposed to activating light this results in destruction of the tissue. Topical ALA application, followed by exposure to activating light (ALA PDT), has been used in a number of dermatologic diseases. [239] Local internal application of ALA has also been used for selective endometrial ablation in animal model systems [240] and in human clinical studies. [241]

Currently there is no commercially available technology and evaluation has not progressed past the initial case reports.

1.3.7.9 ELITT

The ELITT device utilises an intrauterine diode laser that scatters a laser beam around the endometrial cavity. It is a non-hysteroscopic method. It is a non-contact procedure and purports the benefit of treating irregular cavities and difficult to access areas (e.g. the cornua) equally well. [242;243] A RCT comparison of TCRE to ELITT has been reported. [244]: Fifty-eight patients were treated with the ELITT procedure and 58 patients with TCRE. No power study was performed and method of randomization was not described. Endometrial preparation in both arms was with GnRH agonists. At 12 months follow-up, 56% in the ELITT group and 23% in the TCRE group were amenorrhoeic. At 36 months, the figures were 61% for ELITT and 24% for TCRE.

The data is encouraging but at present the device is not commercially available.

1.3.7.10 Review

The extensive evidence of the efficacy of endometrial ablative techniques is testimony to the culture of evidence based medicine. Endometrial ablation offers high patient satisfaction and relief of menstrual symptoms but is still inferior to hysterectomy in these outcome measures. Ablative techniques offer rapid recovery and are more economical than hysterectomy.

With the exception of the trials on MEA, all the above trials on second generation methods were initiated as Phase III trials to obtain Food and Drug Administration (FDA) approval of the device in the USA, and were under the control of the device manufacturers (albeit with the supervision of the FDA). Trial results must be interpreted cautiously and with this fact in mind. The FDA trials almost uniformly use highly restrictive inclusion criteria that reduce the generalisability of the trial results with both doctors and patients receiving financial remuneration for their involvement. The restriction of treatment to only those women who had objective menorrhagia, restricting treatments to only those with small regular cavities (a known positive prognostic factor) will exaggerate outcomes when compared to treatment outcomes achievable when treatment is applied to a clinical population. Many claim the ability to be performed under local anaesthesia but only MEA offers RCT based evidence. The remainder offer observational series that are inherently biased by practitioner and patient bias. Merely saying something can be done does nothing to prove patient acceptability, satisfaction and whether at the end of the day it should be done. To establish the suitability of endometrial ablative techniques under local anaesthesia requires the use of adequately powered, independent randomised controlled trials. To date only MEA offers such evidence.

At present the most thoroughly evaluated second-generation techniques remain MEA and Thermachoice.

1.3.8 Uterine Fibroid Arterial Embolisation

The advances in the field of interventional radiology have created novel therapeutic strategies for the treatment of the symptoms associated with fibroids. Improvements in menstrual symptoms have been reported with significant reductions in objectively measured MBL seen, an effect that is independent of the changes in uterine volume.[245] Arterial embolisation, a technique that was initially utilised in the treatment of solid tumors, obstetric haemorrhage and trauma has been developed and refined over time. Uterine Fibroid Arterial Embolisastion (UFAE) has been demonstrated to have beneficial effects on the size, menstrual effects and pressure symptoms associated with uterine fibroids.

The first reported cases of fibroid embolisation as a therapeutic option was reported from France by Ravina et al. [246] It was used prior to this as a pre-operative procedure to reduce intra-operative bleeding. The first observational series was reported by Ravina's group in the Lancet in 1995. [247] They reported on the first series of 16 who were on the waiting list for open surgery treated with UFAE. With a mean follow-up of 20 months 11 patients reported resolution of their symptoms (with 10 reporting normal menstrual cycles). Three patients reported partial improvement and two required surgery. A variety of series has been reported, often with duplication and overlap as papers report differing aspects of the procedure. The majority of the literature comes from the United Sates, France and England. Most are uncontrolled series and only one RCT has been published. The case series are prone to the biases of case selection and follow-up bias. By 2000 it was estimated that approximately 8,500 procedures have been performed in the United States[248] with the majority of insurance companies reimbursing the procedure. In the UK approximately 2050 UFAE have been performed by 2004 of which the majorities were performed in London and the South West. [249] One centre in London is responsible for 1000 of the procedures.

The technique involves usually a single puncture per-cutaneous trans-catheterisation of both uterine arteries under fluoroscopic control, the selective identification and catheterisation of the tortuous uterine arteries with small, steerable (4 French) catheters. The desired effect is to achieve total or near total occlusions of the arteries by using a combination of contrast agent and the occlusive agent. The most common occlusive agent used is poly- vinyl alcohol particles (PVA). PVA particle vary in size with 300 – 500 micrometers being most commonly used for UFAE. Gel- foam biodegradable foam can also be used as an adjunct to assist in the complete embolisation. There is no attempt to embolise individual fibroids. To minimise radiation dosage to the ovarian tissue modern pulsed fluoroscopy is advised utilising screening rather than diagnostic imaging.

Patient assessment prior to treatment is important. A major concern with UFAE treatments is that the technique, unlike surgery, does not yield a pathological diagnosis. The main concern is that a uterine sarcoma is embolised. The delay in definitive surgery, diagnosis and the attendant adverse effect on prognosis is obvious. Uterine sarcomas are rare comprising only 1% of gynaecological malignancies and 2-5% of all uterine malignancies. [250] Clinically they behave differently from fibroids with their behaviour characterised by an aggressive history, usually women in their 7th decade and arising as a solitary tumour. The Ultrasound Image and Magnetic Resonance Image (MRI) can be useful in making the diagnosis but false negatives occur. Cases of embolised sarcomas have been reported. [251;252, 253]

All types of fibroids seem amenable to treatment with the exclusion of pedunculated sub-serosal fibroids. Reports of bowel obstruction secondary to necrotic subserosal fibroids 'droping off' into the abdomen post UFAE have contraindicated treatment in these circumstances.[254] Infection must be excluded prior to treatment, clinically and usually with screening swabs. Emergency hysterectomies and deaths from overwhelming sepsis have been reported. [255-257] Future fertility is a concern with this technique as the long-term implications are uncertain. Live births have been reported post UFAE. [258;259] There have also been reports of amenorrhoea post UFAE with the majority of these settle spontaneously and represent short term endometrial changes;

however there have also been reports of permanent premature menopause mostly in women over the age of 40 years (2% [4 of 181] in Spies series[260] and 7% [26 of 400] in Walkers series[261]), possibly related to unintentional embolisation of the ovarian arteries through anastomotic utero-ovarian channels.

Pregnancy post UFAE is an interesting issue. The problem with interpreting the number of live births post UFAE is that we have no denominator and no idea how many people were trying to achieve pregnancy. Ravina et al in their case series published in 2000 reported on 5 miscarriages in 13 subsequent pregnancies in a series of 286 (age range 21-53). [262] McLucas data from a series of four hundred women who underwent uterine fibroid embolisation over a four year period give us reasonable data on pregnancy with UFAE. One hundred and thirty nine patients stated a desire for fertility after embolisation. Of these, 52 were <40 years old and seventeen pregnancies have been reported in 14 women with five spontaneous abortions were observed. At the time of writing up ten of the women had normal term deliveries and two women were still pregnant. Carpenter and Walker report retrospective observational data on pregnancies in a series of twenty-nine pregnancies in 671 women who had undergone uterine artery embolisation by one interventional radiologist in a UK district general hospital. [263] Of the 16 deliveries after 24 weeks, fourteen were delivered by caesarean section. There did not appear to be any other major excess obstetric associated risk when the demographics of the population in question is considered

The expulsion of fibroids vaginally has been reported by Park et al [264] and can be a rather dramatic late complication.

The predictive factors affecting outcome of UFEA has been reviewed in a French paper.[265] Eighty-five women who underwent UFEA for the treatment of uterine fibroids were followed up. At a median follow-up of 30 months 17.2% were symptomatic, with 15 requiring further treatment (eight hysterectomies, five hysteroscopic resections for sub-mucous fibroids, one second embolisation and one woman refusing further treatment). The predictive factors for recurrence of symptoms were fibroid size and number. Regarding the time frame for symptom recurrence it is notable that recurrences

occurred after two years. The relevance of late recurrences is that most of the published observational data has follow-up periods of 12 months at the most and thus will under report the incidence of failure and the need for further surgery.

The general lack of good quality trial data is a concern. One small RCT of UFAE has been reported by Pinto et al. [266]The vast majority of the data is retrospective and derived from observational series. The results of REST Study a multi-centre randomised control trial comparing surgery (myomectomy or hysterectomy) with UFAE coordinated by Dr John Moss of Gartnavel General Hospital are eagerly awaited.

Immediate post procedure pain requires a patient controlled analgesia pump and inpatient care for 24 - 48 hours. Some centre advocate prophylactic antibiotics to reduce the risk of infection but this is not evidence based. Uterine Fibroid Embolisation Syndrome (UFES) typically last 2-7 days post procedure and is characterized by pelvic pain, malaise, low grade fever, nausea and or vomiting. It may be difficult to distinguish between infection and UFES and thus many are required to be admitted for antibiotics and observation.

NICE have issued an Interventional Procedure Guidance (No. 94) for UFAE of Fibroids[267] and systematic review commissioned by NICE was completed in March 2004.[249] They comment on the general safety of the treatment in the majority but also note the lack of data pertaining to long-term prognosis, fertility data and avoidance of surgery. They recommend a multidisciplinary team approach incorporating the radiologist and gynaecologist and that all treatments were logged on a database with the Royal College of Radiologist (RCR).

The RCOG and RCR issued a joint statement in 2000 which recommended that the use of UFAE should be viewed as experimental; recruitment should be as part of randomised controlled trials.

Adenomyosis had also recently been treated with embolisation[268] and case reports are encouraging for a condition usually only amenable to non conservative surgery[269]. Many

claim MRI is the best imaging tool for the diagnoses of adenomyosis. MRI criteria that include diffuse or focal widening of the junctional zone as well as bright foci or linear striations within the myometrium on T2-weighted images. On MRI, a focal adenomyoma may appear as a localized low-signal myometrial mass with poorly defined margins that often contain high-signal foci. The sensitivity of MRI and TV ultrasound for diagnosing adenomyosis are comparable in the best hands. Two prospective blinded studies using pathology at hysterectomy as the standard report sensitivities of 70 -78% and specificities of 86 – 93% for MRI with sensitivities of 65 -68% and specificities of 65 – 98% for transvaginal scanning . [69;270]

1.3.8 Laparoscopically Assisted Vaginal Hysterectomy

Minimal access surgical techniques have been developed that allow for Laparoscopic Assisted Vaginal Hysterectomy (LAVH). The technique allows for varying levels of laparoscopic surgery from the dissection and securing the uterine artery pedicle to a complete laparoscopic procedure and allows for the addition of adnexal surgery and treatment of co-morbidities such as endometriosis. The technique has many exponents who extol the virtue of rapid recovery and minimal abdominal scarring. Randomised trial data exists to expand on the previous observational series. [271-275] These trial whilst methodologically an improvement on the observation series are unfortunately mostly small trials, most comparing abdominal hysterectomy with LAVH , usually with single surgeon and thus lack generalisability back to clinical practice. The limited data on LAVH especially versus vaginal hysterectomy has been addressed in the Evaluate trial.

The Evaluate trial group headed by Professor Garry published the results of the largest trial of laparoscopic hysterectomy in 2004. In the same edition they published an economics paper based on the trials work.[276] Two parallel multicentre trials were reported. The first trial comparing LAVH with abdominal hysterectomy in the

abdominal trial, the second comparing LAVH with vaginal hysterectomy in the vaginal trial. The trial was based on 28 UK centres and two centres in South Africa looking at major complication as the primary outcome. Major complication was defined as: major haemorrhage (requiring transfusion); haematoma (requiring transfusion / surgical drainage); bowel, bladder, ureteric injury; pulmonary embolism; major anaesthetic complications; unintended laparotomy and wound dehiscence. A total of 1380 women were recruited with 1346 receiving surgery and 937 completing follow-up at one year.

Women were eligible if they required hysterectomy, had uteri 12 weeks in size or smaller and without significant prolapse (greater than first degree). The randomising surgeon decided which arm – abdominal or vaginal that the patients entered into on clinical grounds. The laparoscopic procedures were a clinically heterogeneous group with laparoscopically assisted vaginal hysterectomy, laparoscopic hysterectomy, laparoscopic supra-cervical hysterectomy and total laparoscopic hysterectomy included.

The abdominal arm of the trial was adequately powered but the vaginal arm was underpowered. In the abdominal arm significantly more patients in the laparoscopic arm had a major complication (mean difference 4.5%, 95% CI 0.9%- 9.1%) with a number needed to treat to harm of 20. In the vaginal arm there was no significant difference in the incidence of major complications although this arm of the trial was under powered and the results were not significant with odds ratios spanning the nil effect. There was no difference in the incidences of minor complications between the study arms. In the laparoscopic arms there was a greater incidence of additional pathology identified (fibroids, adhesions, endometriosis) with the lowest incidence in the vaginal arm. Mean pain scores were significantly less in the laparoscopic arm versus abdominal (adjusted mean pain score 3.9 versus 3.5, mean difference 0.5 at a p value of 0.01). There was no difference in pain scores in the vaginal trial. The mean length of hospital stay was shorter in the laparoscopic versus abdominal trial (3 versus 4 days) and 3 days for each arm in the laparoscopic versus vaginal trial. Quality of life (Short Form 12) was measured at baseline and to 12 months. All trial arms showed improvements in the physical and mental component scores, body image scales, and sexual activity at four

months which persisted at 12 months. There was a significant difference in body image scores at 6 weeks in the laparoscopic versus abdominal route but this was a short term effect with equivalent results at 4 months and no effect seen at 12 months.

The conclusions of the trial were that laparoscopic surgery was associated with a significantly higher rate of major complications than abdominal surgery, took longer to perform(mean 84 minutes versus 50 minutes for abdominal and 79 minutes versus 39 minutes when compared to vaginal hysterectomy). Laparoscopic surgery was associated with faster recovery, less pain and better short term quality of life.

The economic paper published by Sculpher et al [276] in the same journal revealed interesting features. They utilised cost effectiveness analysis at one year expressing their results in QALYs based on the results of the health utility score derived from the EQ-5D at four points from baseline over the year from treatment. Laparoscopic hysterectomy cost £401 (95% CI £271 to £542) more than vaginal hysterectomy with little difference in QALYs (0.015). Compared to abdominal hysterectomy it cost an average of £186 more (95% CI -£26 to £ 375) but this may not be significant. The higher resource use in the laparoscopic arm when compared to the abdominal and vaginal hysterectomy arm were related to the longer theatre time and the use of disposables. When compared to abdominal hysterectomy this was offset by the shorter inpatient stay (mean stay 3.95 vs. 5.11days).

The incremental cost per additional QUALY for laparoscopic hysterectomy was £267, 333 when compared to vaginal hysterectomy and £26, 571 when compared to abdominal hysterectomy. They concluded that costs for laparoscopic hysterectomy were higher than vaginal hysterectomy and closer but still higher than abdominal hysterectomy with the cost per QUALY. The cost per additional QUALY limit of £30,000 set by the NHS in other spheres of health care is breached by the comparison between vaginal hysterectomy and laparoscopic hysterectomy and finely balanced by the comparison with abdominal hysterectomy. A greater use of reusable equipment would present laparoscopic hysterectomy in a more favourable light.

A number of features of this trial deserve closes inspection and certain of these issues have been addressed in the BJOG editorial by Chen et al.[277] Caution must be exercised before accepting the results of this RCT at face value.

Firstly issues of generalisability arise. The allocation of patients into the abdominal or vaginal arm was made on clinical grounds. This allows the creation of allocation bias with the more potentially difficult cases being entered into the abdominal arm, thus skewing the complication rates in those randomised to laparoscopic hysterectomy.

Secondly is the definition of the primary outcome measure of major complication. The outcome measures were composite and could not be equally applied to each arm of the abdominal trial arm. An unintended laparotomy is not possible in the abdominal hysterectomy arm. The progress to open surgery for the laparoscopic arm may be seen as judicious surgery rather than a complication and if the complication rate was adjusted this would cast a much more favourable light over the laparoscopic arms complication rate. If the complication rates are adjusted to exclude unintended laparotomy then the corrected incidences were not significantly different between the laparoscopic and abdominal arms (7.8% versus 6.2% respectively).

Thirdly the individual surgeons in the trial were only required to have experience of 25 laparoscopic hysterectomies prior to inclusion. This does not represent the end of a learning curve [278] for laparoscopic surgery and this difference in experience may bias the results. This raises a training issue.

Fourthly is the heterogeneous nature of the four laparoscopic procedures grouped together under the umbrella of 'laparoscopic hysterectomy'. The range of procedures varied from procedures that were the most technically challenging with a complete laparoscopic hysterectomy with all pedicles taken and the vagina opened laparoscopically to the least invasive procedure of laparoscopic subtotal hysterectomy.

Overall the validity of utilising a RCT to address complication issues is questionable as a study of this kind will always be underpowered to accurately comment on rates of

complications. The trial does allow accurate estimation of effectiveness as measured by differences in QOL scores.

The ACOG recent advice on laparoscopic hysterectomy advises the technique used for hysterectomy should be dictated by the indication for the surgery, patient characteristics, and patient preference. Most patients requiring hysterectomy should be offered the vaginal approach when technically feasible and medically appropriate. If specific additional procedures that can be completed laparoscopically are anticipated before surgery, laparoscopically assisted vaginal hysterectomy may be an appropriate alternative to abdominal hysterectomy. The benefits of laparoscopically assisted vaginal hysterectomy must be weighed against the potentially increased risk and expense of two distinct operative procedures, laparoscopy and vaginal hysterectomy. [279]

1.3.9 Subtotal Hysterectomy

The first recorded hysterectomy was a subtotal procedure performed by Charles Clay in 1843.[167] This procedure remained the chosen method of abdominal hysterectomy for benign indications until the 1950's when the total abdominal hysterectomy predominated. In the 1980's a resurgence in the interest in subtotal hysterectomies occurred fuelled by the work on urinary and sexual function by Kilkku [280-282] and the emerging evidence of the long term efficacy of the cervical screening programme. The procedure benefits from the reduced operative time and morbidity associated with preservation of the cervix uteri. A laparoscopic procedure is also possible.[283] The drawbacks of the procedure are the small numbers who will suffer from light bleeding / spotting from residual endometrial tissue high in the endocervical canal and the fear of cervical cancer in a cervical stump. Hysterectomy rates vary regionally and nationally, so to do methods and the ratio of total abdominal hysterectomy to subtotal hysterectomy.[166;284] A significant decrease in total abdominal hysterectomy and an significant increase in the proportion of subtotal procedure is seen in the US data by Sills

et al. [285] However, 99% still remain total abdominal procedures. Danish data by Gimbel et al revealed a similar trend to the US data. [286] In the Finish data revealed by Vuorma et al the ratios remained static. [287] Overall looking at national figures the Scandinavian countries have the highest ratio of subtotal to total procedures with Sweden having (0.56), the smallest reported ratio is in the UK (0.04).[284]A postal questionnaire of British gynaecologists reported in 1998 by Thakar et al revealed subtotal hysterectomy to be an unpopular procedure in the UK, with seventy eight per cent of female gynaecologists preferring a total hysterectomy for themselves.[288]

Comparisons between the total and subtotal procedure have been made with respect to a variety of outcome. Urinary symptoms, bowel symptoms, pelvic organ prolapse and effects on sex life are assessed.

Urinary incontinence has been assessed in a number of trials.[289-291] The trials vary in size and methodological soundness. The two largest RCT by Thakar and Gimbel give the best quality of evidence. Thakar et al [289] compared subtotal to total hysterectomy in a double blinded RCT involving 279 women followed up for one year. There was no significant difference in urinary frequency between procedures at one year. Both arms showed a reduction in frequency, nocturia and stress incontinence. The frequency of bowel symptoms and measures of sexual function did not change significantly in either group after surgery. The women in the subtotal-hysterectomy group had a significantly shorter hospital stay and a significantly lower rate of post operative pyrexia. In the subtotal arm seven percent of women had cyclical bleeding and two percent had cervical prolapse. They concluded that neither method of hysterectomy adversely affects pelvic organ function at 12 months with subtotal hysterectomy resulting in shorter recovery and fewer short-term complications. The largest trial to date, the Danish RCT by Gimbel et al [292] reported on 349 women randomised to total abdominal hysterectomy (n = 158) or subtotal abdominal hysterectomy (n = 161). Analysis was by intention to treat. A significantly smaller proportion of women had urinary incontinence (the primary outcome) one year after total abdominal hysterectomy compared with subtotal abdominal hysterectomy (9% vs. 18%) [OR 2.08, 95% CI 1.01-4.29)]. Twenty-seven

women (20%) from the subtotal abdominal hysterectomy group suffered vaginal bleeding. Two required removal of the cervix. There was no clinically important differences found between the two hysterectomy methods with respect to the incidence of post-operative complications, quality of life scores (SF-36), constipation, prolapse, satisfaction with sexual life or pelvic pain. This study is the largest to date and methodologically sound and the results are interesting going against the perception that subtotal procedures give rise to less bladder symptoms, long term follow up would be very interesting.

Between 5-20% of women with subtotals will have cyclical bleeding. [290;292] whereas all will be amenorrhoeic after a total procedure. A variety of techniques have been deployed to reduce this number from simple techniques as diathermy to the canal through to radical conisation of the cervix but even then up to 11% will still report symptoms of bleeding. [283]

The incidence of pelvic pain in the literature shows no significant difference between techniques with a generalised reduction in pain seen with both techniques, a similar pattern is seen with respect to quality of life parameters.[289;292-295]

Intuitively one would think that pelvic organ prolapse would be less common after a subtotal procedure as the cervix retains the uterosacral and cardinal ligament complexes. The evidence points to no significant difference but with a trend favoring total abdominal hysterectomy. [284]

The postulated role of the cervix uteri in the physiology of the female sexual response and orgasm in particular has fueled some of the interest in the subtotal procedure. A number of studies of subtotal versus total hysterectomy have reported on sexual functions as an outcome.[280;281;289;296;297] Various parameters including frequency of coitus, dysparunia, orgasm and satisfaction with sexual function have been assessed. The initial work by Kilkku suggested a beneficial effect of subtotal however further randomised and observational studies[289;296;297] have reported no significant difference between the two methods has been found with regards to sexual function. The work of Zobbe et al [296] revealed the predictors for satisfaction with sexual life after hysterectomy

to be a satisfactory preoperative sex life , a good relationship with partner, physical well-being and the use of hormone replacement therapy. Many studies on hysterectomy reveal a reduction in post operative dysparunia with hysterectomy whether total or subtotal.

Overall it would appear that as a procedure subtotal hysterectomy has a lower blood loss than total, takes a shorter time to perform and has less peri and post operative complications (especially pyrexia). On the down side it has a worse effect on bladder function than a total procedure and is associated with a not insignificant incidence of stump related problems. There is no significant difference on the sexual function of patients post total or subtotal hysterectomy.

1.3.11 Conclusion

A number of surgical treatment options are available. Hysterectomy in its various forms remains a very effective treatment for menorrhagia with the highest recorded levels of patient satisfaction but it is associated with a number of common minor complications and a not insignificant number of serious complications. The ever expanding variety of endometrial ablative techniques offer quick easy to learn procedure with high levels of patient satisfaction and a high likelihood of avoiding hysterectomy in the long term. Some offer the ability to be performed under local anaesthesia but few have ever demonstrated this as a primary outcome measure in an adequately powered RCT. Uterine Artery Embolisation offers good relief of a number of symptoms of fibroids but seems particularly good at relieving menstrual symptoms possibly through a local endometrial effect.

1.4 MICROWAVE ENDOMETRIAL ABLATION - AN OVERVIEW

Microwave Endometrial Ablation (MEA ^{TM}) has evolved from a theoretical technology into the most evidence based second generation ablative technology available today.
The purpose of this chapter is to review the scientific basis, evidence base, safety and clinical applications of this ablative technology.

1.4.1 MEA- Scientific Basis and Technical Aspects

Microwaves are part of the electromagnetic spectrum of energy lying between radio waves and infra-red. Microwaves have a wavelength between 0.3 to 30cms and a range of frequency between 300 and 300 000 MHz.
On transmission to tissue the microwave energy causes the water molecules to rapidly change polarity, the resulting oscillations generate thermal energy that results in the clinical effect.
The effect of any thermal energy on a tissue is dependant on the temperature achieved with progressive changes seen in proteins through to irreversible cell death.
The depth of penetration of the microwaves thermal effect is determined by the duration of application, the water content of the tissue and the frequency and wavelength of the microwaves.
All ablative techniques share the ultimate aim of destroying or removing the basal layer of the endometrium. This results in a therapeutic Ashermann's syndrome, alleviating menstrual symptoms. This basal endometrium extends 3-4mm into the myometrium in pharmacologically prepared uteri.[168] The depth of destruction must therefore extend to 4mm, however it must be limited as the total wall thickness in the corneal region may be as little as 6mm.
Any energy source that causes destruction to a greater depth runs the risk of thermal energy reaching the serosa and causing injury to intra-abdominal structures, with the small bowel being most at risk of injury.

Microwave Endometrial Ablation (MEA^{TM}) utilises an 8 mm diameter probe that delivers microwaves of a set frequency of 9.2GHz.
The microwave frequency and wavelength utilised in MEA was specifically chosen so that the total depth of thermal effect matched the endometrial thickness but did not exceed total wall thickness. The power delivered to the tissue is only around 20 watts, approximately equivalent to the energy used to power one small light bulb.

The selected microwaves result in a predictable 3mm depth of direct microwave penetration and a further 2mm depth of thermal transmission. Thus in total a reliable 5mm depth of penetration can be achieved. The microwaves radiate from the tip of the probe in a hemispherical array. The probe itself consists of an aluminium tube which delivers through a ceramic dielectric wave guide the microwave energy that is generated in the magnetron (microwave generator). The energy is radiated in a dielectric hemisphere at the tip of the probe. The probe has two thermocouples, one at the tip to measure the temperature at the tissue surface and a second 10 cm down the shaft of the probe to measure any reflected energy and ensure the shaft does not overheat. The temperature at the tip of the probe is relayed to the microwave unit and displayed as a continuous visual temperature display. This allows the operator to guide treatment of the cavity and maintain the temperature within the therapeutic range of 70 to 80 degrees Celsius that results in endometrial and superficial myometrial cell death. The continuous temperature monitoring also serves as a safety feature in that if temperatures of above 85 degrees Celsius occur an audible alarm will sound and an automatic shut off of the generator will occur once the temperature reaches 90 degrees Celsius. The probe itself is a reusable single piece device that is 338 mm long and 8.5 mm in diameter at the shaft. The probe is covered in a polymer – FEP (Flurinated Ethylene Propylene). The shaft is marked with graduations in whole centimetres. For a distance of 35 mm from the tip a black band extends to indicate the endocervical canal. A yellow band extends for 7mm below the black band and indicates that the tip of the probe is immanent to prevent haematometra formation that can arise from inadvertently treating the endocervical canal. The MEA applicator is attached to the MEA system by two cables. The first is the

coaxial cable that carries the microwave energy from the microwave generator to the MEA probe and a second data cable that relays continuous information from the thermocouples to the consol display and communicates with the chip inside the applicator that stores treatment data and records the number of treatments (set at a maximum of 30 treatments)..

Human endometrium has very high water content and in this respect is very similar to animal liver. A tissues water content is a key factor in the depth of penetration of the microwaves and animal livers provide an ideal model to simulate the clinical effects of microwaves. The initial work on animal livers revealed the predictable depth of penetration of the thermal effect.

In vitro work was progressed to extirpated post -hysterectomy (non-perfused and perfused) uteri utilising vital staining techniques to assess depth of penetration of thermal effect.

A total of 4 non perfused uteri were treated with power settings of 18 watts and treatment times varying between 360 seconds and 510 seconds.[298] Thermocouples measured the temperature at the endometrial and serosal surface. The specimens were processed to assess degree of coverage and the depth of cell death measured using a nitro-blue tetrazolium vital staining technique. From this work it was established that it was possible to limit the depth of necrosis to 5-6 mm without raising the serosal temperature.

Work on 8 extirpated perfused uteri to simulate the heat sink effect of uterine blood flow was performed.[298] This time the power level was varied between 12 and 60 watts over 90 – 960 seconds. The vital staining tests confirmed established that there was no effect on depth of necrosis from blood perfusion. Pre-hysterectomy specimens were utilised with thermocouple monitoring of serosal temperature to establish safety and efficacy in vivo before the first clinical trial on patients.[298] In total 16 pre-hysterectomy treatments were performed with power levels varying between 30 and 48 watts and treatment times varying between 137 and 300 seconds. In these in vivo experiments the bowel was packed away and thermocouple placed on the serosa. No rise in temperature was recorded at the serosa and pathological assessment with vital staining was performed. A

further 3 cases were performed in vivo with the power settings at 30 watts and 40 watts to confirm adequate treatment depths without serosal heating.[298]

From this human data and the animal data the optimal frequency and power settings were selected – 9.2 GHz with an operating power of 42 watts that translates into a tissue power delivery of around 20 watts.

1.4.2 Endometrial Preparation

Pharmacological endometrial preparation can be used prior to MEA but unlike first generation technique it is not an essential. Preparation does allow a predictably thin endometrium, the scheduling of procedures to theatre lists and may improve outcome. The initial RCT evidence from work by Bain and Cooper[299] reported on results using Goserelin (Zoladex) as endometrial pre-treatment in both the MEA and TCRE arms. The centre at Bath reported on utilising suction curettage as a pre-treatment but this is not to be recommended as it may result in unrecognised uterine wall damage (partial perforations / full perforation). The reported bowel injuries shortly after the release of the device into the Australian market is, it is alleged, blamed on a combination of the use of suction preparation, poor training and supervision. Danazol and Goserelin have been used in RCT comparison of MEA under general anaesthesia and local anaesthesia [300]

Whilst some ablative techniques such as Novasure can be used at any stage in the menstrual cycle this does not apply to MEA. Data from Wallage et al [301] established that MEA effectiveness will be reduced if the endometrial thickness is greater than 10 mm.

Post menstrual treatments can be performed in the immediate post menstrual phase when the endometrium is thin after either natural or hormonally induced menstruation.[302]

Current practice at Aberdeen Royal Infirmary is to treat patients after 10 days of medroxypregsterone acetate (Pharmacia, Pfizer Ltd, UK) 10mg twice a day by mouth.The treatment is stopped 10 days prior to the procedure to time menstruation and allows predictable endometrial thickness.

1.4.3 Procedure

Suitable patients are those complaining of excessive menstrual bleeding with a completed family, histologically assessed normal endometrial pathology and a cavity length between 5 and 12cm. Previous myomectomy, classical caesarean section, endometrial malignancy or atypia and active pelvic inflammatory disease are contraindications to treatment. As no fluid distension media is utilised there is no risk of fluid overload and the technology is a blind technique.

Endometrial polyps and non-obstructing sub-mucosal fibroids up to 3cm can be included. Patients require to be fully counselled regarding the nature of the procedure and the clinical outcomes. As with all ablative techniques patients must accept eumenorrhoea as the desired outcome. If amenorrhea is the priority then hysterectomy is to be recommended.

The procedure itself is preceded by an ultrasound scan to measure myometrial wall thickness. A minimum of 10mm thickness to the anterior uterine wall is required before the procedure can be considered. There is a safety concern regards women with a previous lower segment caesarean section having thin anterior uterine walls which resulted in the requirement of an ultrasound scan to show the anterior wall thickness is 10 mm minimum being made by the manufacturers.

As with all ablative technologies patients must be aware of the risk of future pregnancy is such that further pregnancy is not advised and reliable contraception is required post procedure. Concomitant laparoscopic sterilisation can be offered to those undergoing general anaesthesia.

Patients are pre-medicated with a 100mgs of Voltarol (Diclofenac Sodium, Novartis Pharmaceuticals UK Ltd) suppository per rectum one hour pre-operatively. In those with contra-indications to NSAIDS 1 gm (P.R.) paracetamol can be used instead. The technique can be performed under local anaesthesia +/ - conscious sedation or general anaesthesia. The evidence for this will be discussed later in this chapter. The technique of local anaesthesia is that of a four quadrant cervical block (2, 4, 8 and 10 o'clock)

starting posteriorly. 2.2 ml Citanest 3% with felypressin 0.03 unit/mL (Citanest with Octapressin, Dentsply UK) ampoules are delivered to each quadrant through a dental syringe and a 35 mm needle.
Midazolam (to a maximum of 4mg) can be titrated pre / intra-operatively to provide conscious sedation. Intra-operative analgesia 25 – 50 micrograms of Fentanyl (I.V.) can be used if required to achieve short acting rescue analgesic effect. Heart rate and oxygen saturation require to be monitored intra-operatively if sedation and or analgesia are utilised.

The cervix dilated to 9 Hagar, cavity length established and hysteroscopy performed. The cavity must be confirmed as intact and both tubal ostia should be seen to exclude for certain the possibility of a false passage. The utility of ultrasound to ensure correct intra-cavitary placement is not to be recommended. Whilst USS allow for detection of full thickness perforation it will not identify false passage formation or partial thickness perforation. The probe is inserted gently into the cavity and the graduated measurements on the probe must agree with the measured cavity length before treatment can be commenced. The foot pedal is activated once the probe tip temperature of 30 degrees is achieved. The temperature rises is monitored by the control unit and effectively gated by comparing it to data from thousands of previous uncomplicated treatments. Failure to achieve a satisfactory thermal gradient or deviation from the gated results in an automatic shut down and requirement for hysteroscopy to exclude false passage or perforation. Once the probe reaches 50 degrees Celsius the operator is instructed to begin a gentle fundal sweeping action and once in the therapeutic band of 70 -80 degrees Celsius the cavity is then treated, moving the probe from side to side whilst gradually withdrawing the probe to treat the whole cavity. It is undesirable to treat the uterine cervix as this may result in cervical stenosis and haematometra formation on those who continue to menstruate. The tip of the probe is black for a distance of 3.5 cm from its distal end with a yellow band extending for 7mm proximally. The approach of the internal os corresponds to a yellow band appearing at the external os. Treatment is

terminated when this yellow band ends and prior to revealing the black tip of the probe.(See Fig 1.)

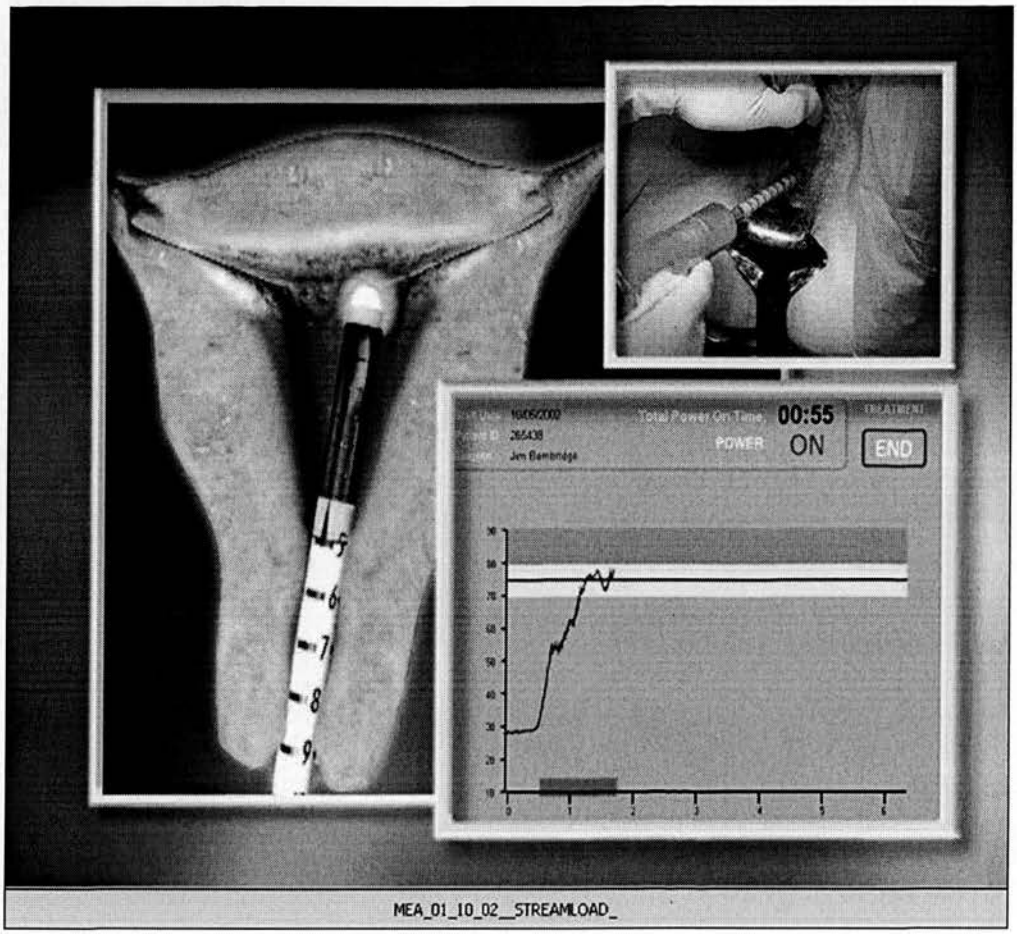


Fig 1 Microwave Endometrial Ablation .
Top right applicator in position. Bottom right instrument display. Left schematic diagram.

1.4.4 Evidence Basis

The initial observational study describing the first 43 women treated with the experimental probe. These first treatments were reported in a paper by Sharp et al from the Royal United Hospital, Bath, UK in 1995.[303]

All women received endometrial preparation (Danazol 800mgms per day or a single Zoladex implant for 4 weeks prior to surgery). The mean treatment time was 2 min 12 sec (range 50-310 sec). 6 months after treatment the quoted success rate was 83%, 13 patients (57%) were amenorrhoeic, and six (26%) were experiencing light menstruation. They reported the technique as safe and easier and quicker to perform than current alternatives.

The paper was followed up with a second paper published in 1999 that included clinical follow up to 3 years. [304] The treatments were performed between October 1994 and April 1995, all patients had failed to respond to medical treatment. Follow-up assessment was by a statement of perceived menstrual loss and satisfaction supported by a menstrual symptoms questionnaire score. The rapid technique (mean treatment time of 141 seconds reported) was much faster than comparable first generation ablative technologies. Amenorrhea was observed in 37% and very light periods/discharge was seen in 26 %. Overall satisfaction at three years was reported as 84 %. Significant reductions in dysmenorrhoea were reported at three years. Three re-treatments and four hysterectomies had taken place by three years. The technique was also described as easier to learn with a very short learning curve avoiding the risks of fluid overload, operative haemorrhage and earthing problems.

In the age of evidence based medicine no matter how promising the results of an initial study, any claims made based on observational non-randomised data requires to be backed up with good quality evidence. Ideally this should be from methodologically sound randomised controlled trials. This evidence will be reviewed.

1.4.5 Comparison to Gold Standard

The 'Gold Standard' for ablation technology is Trans Cervical Resection of the Endometrium (TCRE). This technique has been validated against hysterectomy in a number of trials. MEA™ has been compared to TCRE in a randomised control trial by

Cooper et al.[223] Follow-up data at one, two and long-term data to 5 years will be discussed.

The study randomised 263 women referred for endometrial ablative surgery to MEA^{TM}. The study was powered to give 80% power of demonstrating a 15% difference in satisfaction with treatment. All procedures were done under general anaesthesia after endometrial thinning. At 12 months, 89 (77%) women in the MEA group and 93 (75%) in the TCRE group were totally or generally satisfied with their treatment and 109 (94%) versus 112 (90%) found it acceptable.

Despite very rapid TCRE procedures the mean operating times were significantly shorter for MEA^{TM} than for TCRE (11.4 vs. 15.0 min, p=0.001) and the postoperative stay slightly but not significantly shorter. Quality of life data was assessed using SF-36. Of the eight health-related quality of life dimensions, all were improved after MEA^{TM} (six significantly) and seven were improved after TCRE (all significantly). Both techniques achieved high rates of satisfaction and acceptability and both improved quality of life after 1 year. However the study was inadequately powered to exclude a difference in satisfaction between the groups of less than 15%.

Follow-up to 2 years by Bain et al revealed durable results with 249 (95%) of the original patients returning questionnaires at 2 years. [299] Menstrual status in both groups was similar, although the amenorrhea rate was higher after microwave endometrial ablation. Seventy-nine percent of women were either completely or generally satisfied after microwave ablation compared with 67% after transcervical endometrial resection. Health-related quality-of-life scores remained higher than at recruitment for both treatments. Hysterectomy rates were similar at 2 years (11.6% after microwave endometrial ablation and 12.7% after transcervical endometrial resection), and no repeat endometrial ablative procedures were required.

Recent long-term data to 5 years was presented initially as a conference proceeding at the America Association of Gynaecological Laparoscopists in Las Vegas in November 2003 and subsequently published.[305] A total of 236 (90%) were followed up to 5 years

(116 MEA™ arm, 120 TCRE arm). Menstrual status in both groups was similarly and significantly improved. Amenorrhea was reported by 65% after MEA™ versus 69% after TCRE (p = 0.751). Significantly more women reported themselves totally or generally satisfied with MEA™ compared to TCRE (86% percent versus 74%, p= 0.017). Significantly more women in the MEA™ arm reported their treatment as acceptable (97 % vs. 90%, p= 0.03). Health-related quality-of-life scores remained higher than at recruitment for both treatments. Hysterectomy rates at 5 years were 16% after microwave endometrial ablation and 25 % after transcervical endometrial resection (p= 0.09).

They concluded that Microwave endometrial ablation is an effective long-term alternative to transcervical endometrial resection for dysfunctional uterine bleeding.

1.4.6 Local Anaesthesia versus General Anaesthesia

The evolution of ablative technologies includes the assessment of the technologies under different anaesthetic regimes. General anaesthesia is the predominant anaesthesia utilised with first generation technologies of TCRE, Rollerball Endometrial Ablation and Endometrial Laser Ablation. The rational of moving to a local anaesthesia treatment includes the benefits to a healthcare system and its recipients of freeing up theatre / anaesthetic time and staff and the proven safety benefits of local over general anaesthesia. The move to local anaesthesia if proved possible would be a keystone in the development of an outpatient treatment. First however the suitability of a technology under local anaesthesia must be demonstrated on an unselected population in a adequately powered randomised controlled trial with acceptability as the primary outcome.

Many ablative technologies can claim that they can be performed under local anaesthesia but lack robust evidence based on RCT evidence in an unselected non biased population.

Wallage et al assessed the suitability of MEA ™ with women randomised to local anaesthesia (L.A.) or general anaesthesia (G.A.).[300] The trial included a patient

preference arm where patients were allocated their anaesthesia of choice. All patients received pharmacological endometrial thinning (Zoladex or Danazol) and were performed in the operating theatre. This trial addressed the key questions of whether it was possible to perform MEA ™ on unselected patients and whether patients found it acceptable. 180 patients were required to give be randomised to give a 85% power to detect a 15% reduction in acceptability. The level of acceptability was derived from a known acceptability of 93% for women under general anaesthesia generated by a previous RCT. 322 procedures were completed in the trial.

91% of treatments commenced under L.A. were completed under L.A. Women with a preference for local anaesthesia were especially likely to be completed under local anaesthesia. In conclusion 69% of women would consider MEA ™ under local anaesthesia (either expressing a preference or willing to be randomised to L.A.), 87% of patients found MEA ™ under L.A. totally or generally acceptable and post operative recovery details (time to discharge, nausea, analgesic use, return to work or normal activity) were similar for both L.A. and G.A. Despite this only 75% of those randomised to L.A. would have their treatment the same way, significantly less than those randomised to GA (88%).

When analysing factors that predicted success under local anaesthesia they looked at baseline hospital anxiety and depression scores, previous vaginal delivery, dysmenorrhoea scores and previous LLETZ (Large Loop Excision of the Transformation Zone). None of these factors predicted success under L.A. This study revealed the potential of the technology to be performed acceptably under local anaesthesia and opened the door to the possibility of moving the technology out of theatre into the outpatient department.

1.4.7 Assessment of Outpatient Post Menstrual Treatment.

The author undertook a randomised controlled trial to evaluate outpatient post menstrual treatment under local anaesthesia which will be discussed in a subsequent chapter.

1.4.8 Comparison to IUS

As ablative technologies have moved towards treatment under local anesthesia often in an outpatient setting it becomes increasingly valid to make comparisons to the Mirena Intrauterine System. A study by Henshaw et al in Southern Australia compared MEA ™ with Mirena in the management of heavy menstrual bleeding.[306]

The conclusions from this study are limited by the study design which was a retrospective cohort study. Thirty-nine women were treated with MEA ™ and 23 women with Mirena, with the mean duration of follow-up to 14.6 months. Acceptability of the treatment process and satisfaction with outcomes was very high for both procedures. Each treatment led to a statistically significant reduction in menstrual bleeding ($p < 0.0001$) and dysmenorrhoea scores ($p < 0.002$). There were no statistical differences between the two treatments for any of the primary or secondary outcome measures assessed (Primary measures included acceptability of the treatment process, effectiveness of the treatment, and satisfaction with outcomes. Secondary measures included side effects, complications and quality of life [SF-36]).

They concluded that the treatments seem equally effective in the management of heavy menstrual loss.

Prospective adequately powered randomised controlled trials are desperately needed to compare Mirena IUS with MEA ™. Unfortunately they are very difficult to recruit for and as Rogerson et al discovered in the SMART trial. [307] The SMART trial was multi-centred and methodologically sound and should have by rights succeeded but for the unexpected strong preferences expressed by women approached for either IUS or ablation such that the women would not accept random allocation.

1.4.9 Safety

The safety of any endometrial ablative technologies is crucial. The safety of first generation endometrial ablative technologies has been established in two national audits reported (Mistletoe study and Scottish Hysteroscopy Audit Group [173;210]). The second generation technologies are not yet sufficiently widespread and complications too infrequent to allow for large national audits and thus safety data must come from smaller audits, prospective series and case reports. Parkin reported [308] a prospective series of 1400 consecutive cases. The data covered 13 gynaecological units in the UK and Canada. Out of 1433 cases one major complication of small bowel damage occurred giving an incidence of 0.7/1000. There were few minor complications and he concluded that MEA™ appeared at least as safe if not safer than first generation hysteroscopic methods. A satellite symposia held in conjunction with the American Association of Gynaecological Laparoscopists 32nd Annual Meeting commented on the safety of second generation ablative technologies in general and MEA ™ in particular. [309] The MAUDE database of the United States Food and Drug Administration [310] was analysed in July 2003 and revealed 46 reports of bowel injury associated with the Thermachoice device, 2 associated with the HerOption, 1 with the Hydrothermablator and 9 with Novasure. The incidence of major adverse events in the over 18,000 MEA ™ treatments to date was reported as 27 cases (22 bowel injuries). It would appear that no ablative technology is without risks. The sub-analysis of the 27 adverse events with MEA ™ reported that 4 (15%) of the cases were contra-indicated (e.g. repeat MEA ™ , endometrial pre-treatment suction aspiration, treatment continued despite discrepancy between measured cavity length and probe depth), 3 (11%) would have been screened out as unsuitable by ultrasound measurement of uterine wall thickness, 19 (70%) could reasonably be expected to have been picked up by post dilation hysteroscopy and 1 remained undetermined (salpingitis). The effect of improved operator training and revised manufactures instructions for use resulted in 6640 treatments without incident between November 2002 and July 2003.

1.4.10 Assessment of MEA versus Fluid-filled Thermal Balloon Ablation– the NICE Report

The National Institute for Clinical Excellence (England and Wales) has recently published its Technology Appraisal Guidance No 78. [311] The guideline was based on the evidence submitted both by device manufacturers, expert groups/ bodies and the Assessment Group by the Garside et al of the Peninsular Technology Assessment Group of the Universities of Exeter and Plymouth, UK.[312]

This guidance asserts that both fluid filled balloon ablation (Thermachoice / Cavatherm) and Microwave Endometrial Ablation are recommended as treatment options for heavy menstrual bleeding when a woman and her clinician decide that surgical treatment is indicated. The similar abilities of both technologies to restore periods back to a normal level (eumenorrhoeia) were stated. The versatility of MEA over a wider range of cavity types (5-12cm cavity lengths / polyps / non-obstructing fibroids up to 3cm) was noted with Thermal Balloons being restricted to 4-10cm regular cavities. The higher amenorrhoea rate associated with MEA^{TM} was noted. The individual indications for each technology were reviewed and it was recommended that the decision as to which treatment to use was to be made jointly by the woman and the clinician responsible for treatment. The decision should be made after an informed discussion taking into account the desired outcome of the treatment (such as reduced menstrual bleeding or complete cessation of menstrual bleeding [amenorrhoea]), the relative benefits of all other treatment options and the adverse events associated with them, as well as the clinical condition, anatomical suitability and the individual preferences of the woman.

The Assessment Group's economic assessment utilized a Markov model, which examined the progress of six hypothetical cohorts of women with HMB treated separately by TBEA, MEA, TCRE, TCRE and RB, RB, or hysterectomy. Taking the perspective of the NHS they calculated incremental cost utility between different treatment options over a 10 year period. This model concluded that the second-generation techniques (MEA and TBEA) are more cost effective than the first-

generation techniques (TCRE and/or RB). Although base-case analysis showed that TBEA dominated MEA, the overall differences in costs and utilities were negligible, and moreover the results were sensitive to small changes in utility values.

In the NICE assessment they estimated that 26,000 hysterectomies are performed in the UK each year for menorrhagia and a further 16,000 endometrial ablations are carried out, of which about 2000 are performed using second-generation techniques. The Assessment Group estimated that if all hysterectomies were replaced by EA, the annual cost saving would be of the order of £29 million, (divided 50: 50, first generation: TBEA / MEA). Under a hypothetical scenario of all hysterectomies being replaced by second-generation endometrial ablation techniques, the cost saving would be even greater at more than £32 million per annum.
They commented on the lack of head to head comparisons between the two second generation technologies. A Randomised Controlled Trial funded by the Chief Scientist Office comparing the two technologies is in progress in Aberdeen and due to report in 2006/7.

1.4.11 Conclusion

The technology of Microwave Endometrial Ablation has solid evidence based in pragmatically designed randomised controlled trial data. The treatment is approved of by the National Institute for Clinical Effectiveness. The technology is suitable for the majority of women who present with the complaint of excessive menstrual bleeding. The treatment is effective and acceptable to patients giving high levels of reported satisfaction. It has long term follow-up data comparing it to the gold standard of TCRE and has been proven in RCT's in a variety of clinical scenarios and situations under general anaesthesia, local anaesthesia and post-menstrually in an outpatient environment without loss of clinical or economic effectiveness

Summary of Chapter 1

The published literature reviewed in chapter 1 demonstrates the body of knowledge thus far as it relates to excessive menstrual bleeding, its epidemiology, aetiology and treatment options -both medical and surgical.

There are a number of areas that require further assessment. The question of where ablative procedures stand in the hierarchy medical and surgical treatment options for menstrual problems remains to be answered. There is a complete lack of long term data on the outcome of patients managed medically for their menstrual problems and this gap in knowledge needs to be closed. These questions will be addressed in chapter 2 which looks at the long term outcome of women randomised to medical treatment or TCRE.

The established evidence for first generation ablative techniques has been presented. MEA has been already been compared in a RCT to endometrial resection (TCRE). TCRE is not the commonest ablative procedure world wide. In many countries and in North America in particular rollerball (RBEA) remains the most popular method of ablation. A randomised comparison of MEA and RBEA is desirable and this is presented in chapter 3.

Outpatient treatment was never feasible with 1st generation technologies however many see it as a natural progression for many of the 2nd generation techniques with the attendant benefits on precious healthcare resources. Before such treatment is established it needs to be assessed in a RCT to assess outcome in a non biased and unselected population. Patient centred outcome measures of acceptability and satisfaction with a treatment require to be proved as does the economic impact. A randomised comparison of MEA in both standard treatment under GA and treatment in a genuine outpatient environment will be assessed in Chapter 4.

The impact of endometrial ablation on hysterectomy rates is often disputed. Some argue that ablative procedure only delays the inevitable definitive surgery of hysterectomy and as such 'interim operations' will only increase the health service costs in the long-term. This impact is assessed both locally (Grampian) and nationally (Scotland) in chapter 5.

CHAPTER 2

Five-year follow-up of women randomised to medical management or transcervical resection of the endometrium for heavy menstrual loss; clinical and quality of life outcomes.

2.1 Introduction

Twelve percent of all referrals to a gynaecologist are for the complaint of heavy menstrual bleeding [313] whilst the estimated cost to the National Health Service of medical treatment for the complaint in the UK in 1995 was £7 million [100]. There is considerable uncertainty about how best to treat women suffering from excessive menstrual loss with the numerous medical treatments available failing to control a high and rising hysterectomy rate in the UK. Figures from an observational study by Coulter et al [314] revealed that within five years of referral to a gynaecologist with menstrual problems 60% of women will have a hysterectomy and only 12% are maintained on medical treatment.

The majority of medical trials of treatments for menorrhagia take an explanatory rather than pragmatic format. The trials are uniformly short in time scale (prior to the 2 year follow up of this study there was no RCT trial data on medical treatment longer than 6 months).

The majority of trial data on medical treatment involves only 2 to 3 cycles of active treatment before cross over to either placebo or an alternative medical therapy[53;124;134;135]. These trials have inclusion criteria that restrict the trial data to women with objective menorrhagia as estimated by either PBLAC or the Alkaline Haematin Test. As a result generalising the trial results back to a clinical population where up to 50% may have subjective menorrhagia is dubious.

It is well established that excessive menstruation has a deleterious effect on a sufferer's quality of life[15;181]. Coulter et al reported data from primary care.[315] They performed a prospective cohort study of patients consulting a general practitioners complaining of excessive menstrual bleeding. Patients managed medically were significantly more likely to be dissatisfied with their treatment than those in the surgical group (21% vs. 5%). Those with severe symptoms gained no benefit in quality of life if treated medically whereas those in the surgical arm experienced significant improvement. Despite the known deleterious effects on quality of life there is a paucity of data on the long term effect of medical treatment on a patient's quality of life. Outcome measures used in the existing medical trials focus on the reduction in measured blood loss, drug associated side effects and subjective reduction in bleeding. This study will assess the long-term satisfaction, acceptability and quality of life outcomes in both the medical and surgical arms. Rates of subsequent surgery will be evaluated.

Endometrial ablation has been established as an effective alternative to hysterectomy[188;189;191;193]. Two major national audits have confirmed the safety of the technique [173;210]. Long term data are available from one randomised trial assessing hysteroscopic surgery [192], for women who were initially referred for hysterectomy.
Despite the many benefits of ablative procedures not everyone is convinced of the merits of wide spread usage of the technology. Concerns that it may in actual fact increase the hysterectomy rate rather than decrease it , possibly through an effect of lowering the threshold for surgery [316;317].

The purpose of this trial was to assess the long term follow up of the original trial participants. Short (4 months) and medium term (two years) results comparing medical management with TCRE have been published [15;181] . The results of the patient preference arm have also been reported [187].
The five year results are now presented for this trial focusing on patient satisfaction, acceptability, menstrual status, changes in health related quality of life, and rates of

subsequent surgery. It is important to note that the Levonorgesterol intrauterine device (Mirena) was not licensed as a treatment option at the time of the trial

2.2 Methods

Ethical approval was sought and obtained from the local area ethics committee. The trial was designed to compare, in a RCT format medical management and TCRE for women complaining of heavy menstrual loss. The women also had to have no preference for either medical or hysteroscopic management (the patient preference trial analysed those with an expressed preference). Eligible women were recruited from the general gynaecology clinics of nine consultant gynaecologists between October 1994 and September 1995. Women were eligible if they met the following entry criteria: consulting a gynaecologist for the first time with a complaint of heavy menstrual loss; family complete; a clinical diagnosis of dysfunctional uterine bleeding (uterus less than ten weeks' pregnancy size and normal endometrial pathology); and had not been referred specifically for surgery.

One hundred and eighty seven (69%) from 272 eligible women consented to randomisation in a 1:1 ratio, 94 being allocated to medical treatment and 93 to transcervical resection. Randomisation was by computer generated random numbers in balanced blocks of twenty. Allocation was achieved by opening sealed, serially numbered, opaque envelopes. The majority of those who refused randomisation had expressed a preference for one or other treatment and were evaluated separately in a patient preference trial [187].

In keeping with the pragmatic nature of the trial patients were not routinely scanned or hysteroscoped prior to inclusion into the trial, nor was there any attempt made to objectify or semi –objectify the menstrual loss.

Medical treatment was prescribed by the patient's own consultant and had to be a recognised treatment for menorrhagia with which the patient had not previously been

treated. The treatment was to be continued for at least three cycles. Treatments prescribed were: Tranexamic Acid (1gm four times a day) for the first five days for women with regular periods with Mefenamic Acid (500mgs three times a day) added if there was dysmenorrhoea ;Combined Oral Contraceptive Pill (30 micrograms second generation pills); Danazol 200mgs continuous for 90 days; Progestogens were prescribed for heavy irregular periods day 12 -25 (day 5 -25 if associated dysmenorrhoea) if they declined or were contra-indicated from receiving the COCP or Danazol.

The majority of TCRE's were performed by the research registrar (Dr K G Cooper), the remainder by three consultants. TCRE's were performed using a combined resection / ablation technique. A 7mm 90 degree resection loop was used to resect the anterior, posterior and lateral walls. Rollerball was used to ablate the fundal and cornual regions. The endometrium was pre-treated with a subcutaneous 3.6 mg gonadotrophin releasing hormone analogue (Zoladex) 5 weeks prior to surgery. All procedures were performed under general anaesthesia with urological glycine (1.5 %) as distension media. After follow-up at four months, all recruits, irrespective of initial management, could request further and /or different treatment. This policy reflected normal clinical practice in keeping with the pragmatic [15;181] design of the trial.

Patients were in the initial trial results reviewed at 4 months by the research fellow with postal follow up at two years as published [15;181].

Postal questionnaires were sent five years after initial treatment (with telephone follow-up of non responders), assessing gynaecological symptoms, satisfaction with treatment, and acceptability of management. Changes in health related quality of life were measured using the Short Form-36 health survey (SF-36). Subsequent treatments were also determined, both from the questionnaire and from the hospital surgical database. As Aberdeen Royal Infirmary is the only hospital with a gynaecological service for the district, we can be certain of further hospital treatment received for those who failed to respond to the Grampian region of Scotland.

2.2.1 Statistics

The original sample size calculations indicated that 180 randomised women would be required for the study to have 80% power to detect an absolute difference in satisfaction with treatment of 20% at the 5% level of significance[19]. Analysis was by intention to treat with patients analysed according to initial treatment allocation. SPSS for Windows (Version 8) was used for data entry and statistical analysis. Independent and paired t tests were used to analyse continuous variables (independent and related) with a normal distribution. The Mann Whitney U test was used for ordinal or continuous variables that did not have a normal distribution. Independent nominal data were analysed using either the Chi-squared test or Fisher's exact test, depending on sample size. McNemar's and the Wilcoxon Signed Rank test were used for paired nominal data describing dichotomous and related variables, respectively. 95% confidence intervals were calculated for differences in means and proportions using the Confidence Interval Analysis programme (version1.1).

2.3 Results

One hundred and eighty-seven women were originally randomised between October 1994 and November 1995, 94 to have medical treatment and 93 to TCRE. Postal follow-up questionnaires were sent five years (range 59 to 63 months) after initial treatment and were completed by 144 (77%) women, 71 in the medical group and 73 in the TCRE group. Eleven of the forty-three not followed up were known to have left the region. Operative details for the five years (from the hospital databases) on the other thirty-two who failed to respond, but had not left the region, are included. The trial profile is shown in figure 1.

2.3.1 Participants

Table 1 summarises the baseline characteristics of those successfully followed up: they were very similar to the original trial group[12]. Baseline SF-36 scores were also comparable for each group and globally reduced relative to women of the same age in the general population [20](Table 2).

2.3.2 Subsequent treatment received by five years

Operative data were obtained from returned questionnaires and verified from the hospital surgical database. Only 13 women had left the region by five years but any operations they had received prior to their departure were recorded. Subsequent management is summarised year on year in figure 2.

At five-year follow-up, 7/70 (10%) of those randomised to the medical arm were still using medical treatment. Seventy-two of the 94 recruits (77%) had undergone surgery; 54 had a TCRE, one a TCRE with a further repeat ablation, 15 had undergone hysterectomy, and two a TCRE plus further hysterectomy. Twenty five (27%) women allocated to TCRE had undergone further surgery; 7 repeat TCRE's, 15 hysterectomies

and 3 repeat TCRE plus hysterectomy. Hysterectomy rates after five years were 18% and 20% for medical and TCRE arms respectively. Over 70% of further surgical procedures occur within two years of having a TCRE.

2.3.4 Menstrual status at follow-up

Changes in menstrual symptoms at five years are shown in Table 3. Both trial groups have a highly significant and comparable reduction in bleeding and pain scores. Significantly fewer women in the medical arm were amenorrhoeic or had very light periods (spotting / bleeding score from 1 to 5), than in the TCRE arm (66% compared with 84%) whilst more women in the medical arm regarded their menstrual status as unchanged or heavier (13% compared to 4%). Significant reductions were present in three of the five pre-menstrual symptoms in the medical arm, as at two years. Significant reductions occurred for all five pre-menstrual symptoms in the TCRE arm.

2.3.5 Satisfaction / Acceptability

These results are shown on table 4. Compared with the medical group, women allocated TCRE were significantly more likely to be totally satisfied at five years. Those actually dissatisfied with their treatment were low in both arms (10% medical, 5% TCRE). Acceptability levels were very high in both groups at five years although only 20% of women allocated to medical treatment would recommend this form of treatment, compared with 79% in the surgical arm who would recommend TCRE ($p<0.001$, difference –73% to –45%). Notably, of the 71 women in the medical arm who returned questionnaires at five years, 45 had undergone TCRE and 36 (80%), of these would recommend this form of treatment.

2.3.6 Health related quality of life

The effect over time on QOL scores is shown in Figure 3.Baseline and five year SF-36 follow-up data are presented for those who completed both questionnaires (Table 2). The changes in SF-36 scores were higher for all eight health scales at five years for those allocated TCRE, and significantly so for three of them. Seven of the variables were improved, four significantly, from baseline for those in the medical arm. In the TCRE group, all eight health scales were significantly improved from baseline, achieving scores similar to normative values for a healthy female population of equivalent age[20]

2.4 Discussion

This study represents the longest follow-up of women participating in a randomised trial of medical treatment for heavy menstrual loss and also of women undergoing TCRE who were not initially referred for surgical treatment of their periods. As the randomised cohorts are made up of women who were ambivalent to what treatment they received at outset as those with a treatment preference were identified and studied separately [187]. Thus the potential for motivational bias to cloud the results has been removed and any impact from allocation of the original trial of "resentful demoralisation" [318] is negated . The treatment progression in both cohorts observed is a genuine response to that treatment group allocation. This is the first time long term treatment data have been presented for women with heavy menstrual loss in anything other than an observational study. More importantly this trial demonstrates the impact that endometrial ablative surgery can make on the high hysterectomy rates previously quoted [314].

Follow-up questionnaires were not obtained from 45 women from the randomised cohort, eleven of whom had left the region. Since this is the only hospital offering gynaecological services in the area, information was available on operative procedures, general practitioner correspondence, and subsequent clinic attendance for 34 of the 45

women who remained in the region. The subsequent treatments received by these women were comparable in type and number to those who returned questionnaires, for each trial arm, and failure to obtain personal follow up should not affect the generalisability of the results. We do acknowledge that the numbers required to fulfil the initial power calculations have not been achieved. Nevertheless the difference observed in those satisfied (22%), was of the size originally sought and the difference was statistically significant at the 1% level.

2.4.1 Medical arm

Medical treatments allocated at baseline were all recommended treatments, and no treatment proven to be ineffective was prescribed. Some may argue that optimal results with medical treatment occurs if the original blood loss is objectively pathological, which was not determined, but this also applies to endometrial ablation[19]. Only 10% of women initially allocated to take medical treatment continued to take this at five years, similar to the study by Coulter et al [314], whilst 77% have undergone surgical treatment for heavy menses by this time. Individual medical treatments used by women at follow-up were not determined as the numbers were so small and it was the aim of the trial to evaluate a medical policy rather than identify optimal medical treatment. We are unable to address the numbers not using medical treatment because they are satisfied with their menses. Such a number would be expected to be small as 87% are already accounted for (77% having surgical treatment and 10% continuing medical treatment). Those totally satisfied with their treatment were significantly fewer than amongst those allocated to TCRE, although bleeding and pain scores, and treatment acceptability were comparable to the TCRE arm. Other menstrual parameters were also significantly improved whilst pelvic pain remained low and equivalent in both arms. The results are generally similar to those at two years, but much improved from the four-month results. This may be due to the 77% of women in this arm who underwent TCRE or hysterectomy. The fact that only 20% of those initially allocated medical treatment would recommend it, compared

to 80% of those who subsequently had a TCRE from this group, who would recommend TCRE, suggests that surgery has improved the medical arm results.

A significant fact is that the most effective medical treatment available the Mirena coil, was not licensed for treatment of menstrual dysfunction when this trial was initiated. Mirena offers an attractive medical alternative, particularly for those wishing to maintain fertility. Barrington et al [183] have compared the Mirena IUS to Thermachoice Endometrial Ablation in a small RCT. The trial has significant methodological failings however they concluded that Mirena offers similar menstrual benefits to TBEA. These conclusions remain to be proven in a well constructed randomised trial whether it is as efficient and effective as endometrial ablation. An attempt to undertake a well constructed trial in the UK had to be abandoned through failure to randomise women due to strong preferences, particularly for endometrial resection, despite this being under general anaesthesia [307].

2.4.2 Surgical arm

27% of women in the surgical arm have had further surgery by five years. Importantly, few further procedures are performed after two years following TCRE, irrespective of trial group. 20% of the TCRE cohort has had a hysterectomy, which is similar to the proportion (18%), in the medical arm and can reassure us that a policy of early endometrial ablation does not lead to an increase in hysterectomies. This rate is much lower than the 60% hysterectomy rate reported after five years from observational study undertaken before the widespread uptake of ablative surgery[314].

Rates of satisfaction with, and acceptability of treatment, remain high, correlating well with the numbers who would recommend TCRE (79%) as treatment for heavy menstrual loss. Bleeding and pain scores and number of heavy days remained highly significantly better than at recruitment, similar to short and medium term follow up, with only the number of days heavy bleeding significantly less than amongst those in the medical arm.

Pre-menstrual symptoms remain significantly reduced from baseline although the reason for this remains unknown.

The fact that contraception is required post ablation has raised the question of concomitant hormonal contraceptives adding to the menstrual effect of ablated patients. This was not assessed in the trial given its pragmatic nature but previous studies form Aberdeen confirm a large percentage (60- 65%) of couples in previous RCT of ablation are sterilised (male or female) and thus not using or requiring any hormonal contraceptive. [191;192;213]

2.4.3 Health related quality of life

This trial represents the longest term evaluation of change in health related quality of life for women with heavy menstrual loss managed medically or surgically. The effective health care group[100] recommended that measurement of changes in health related quality of life should be performed when assessing treatments for menorrhagia. Heavy menstrual loss is known to cause significant deterioration in general health and quality of life[15;319;320]which has been overlooked when evaluating treatments for this condition, particularly medical. At baseline SF-36 scores are globally and markedly reduced. After five years in the TCRE arm SF-36 scores were returned to and maintained at near normative levels[321] and are all significantly improved from baseline. Women in the medical arm also had improved SF-36 from baseline levels for seven of the eight variables at five years, four of these significantly. The values achieved are lower than those in the TCRE arm and also remain lower than normative values (Figure 3).

2.5 Conclusion

At five years, women allocated to TCRE remain in better health than those initially managed medically. This clearly demonstrates that women treated immediately with TCRE achieve higher rates of satisfaction, better menstrual symptom relief, and greater improvements in health related quality of life than women initially allocated

medication. Also of note those who received TCRE in the surgical arm had greater health related quality of life scores even when compared to those in the medical arm who subsequently received TCRE. Regarding medical treatment after five years few women are still being maintained on medical treatment and the vast majority of women, around 80% in both arms have avoided a hysterectomy.

This study provides evidence that first line medical therapy may not be justified. It would seem that a policy of early endometrial ablation using a proven technique to women who are ambivalent about their treatment for heavy menstrual bleeding will improve their outcome. Women managed by such a policy would be more likely to be satisfied, have less menstrual loss and have no greater risk of hysterectomy than those initially managed medically. A subsequent decrease in hysterectomies could be expected.

The results therefore consolidate the conclusions drawn from the four-month and two year data. The findings apply to women attending a gynaecologist for the first time for treatment of heavy menstrual loss, who do not have a treatment preference. Early recourse to endometrial ablative surgery will afford these women better relief of symptoms and improvements in health related quality of life.

With more simple, but equally effective endometrial ablative options such as Microwave ablation[299] and the thermal balloon:[219;220;322] now available, all hospitals offering a gynaecological service should offer eligible patients a proven endometrial ablative technique once referred to a gynaecologist for treatment of heavy menstrual loss.

Crucially this trial allows the establishment of a hierarchy of treatment options for excessive menstrual bleeding. Hysterectomy is superior to endometrial ablation offering guaranteed amenorrhoea, the highest recorded satisfaction but at the greatest treatment cost. Endometrial ablation in the form of TCRE is superior to medical treatment (excluding the Mirena IUS). Eligible women referred from primary care can now be offered effective treatment in the form of endometrial ablation without first having to 'earn it' by failing to respond to medical treatment.

Table 1 Baseline characteristics of those followed up at five years. Values are numbers (percentages) of women unless stated otherwise

	Randomised Medical (n = 71)		Randomised T.C.R.E. (n = 73)	
Mean age (S.D.)	41.8	(5.2)	41.6	(5.1)
Mean weight, Kg (S.D.)	66.9	(13.30	68.2	(14.1)
Mean haemoglobin g/dl (S.D.)	12.79	(1.16)	12.61	(1.66)
Menstrual symptoms				
irregular periods	39	(55)	40	(55)
3 - 5 days bleeding	11	(15)	9	(12)
>5 days bleeding	57	(80)	60	(82)
mean no. days heavy bleeding (S.D.)	4.42	(2.02)	4.14	(2.44)
regular dysmenorrhoea	38	(54)	37	(51)
Menstrual symptom rating scale				
severe	42	(59)	41	(56)
very severe	21	(30)	26	(36)
Bleeding score - mean -(S.D.)	24.29	(8.72)	25.09	(7.3)
Pain score - mean -(S.D.)	14.23	(9.55)	13.48	(10.39)
Premenstrual symptoms				
bloating	50	(71)	59	(81)
breast discomfort	48	(68)	52	(71)
irritability	49	(69)	53	(73)
headaches	44	(62)	44	(60)
depression	35	(49)	40	(55)
Dyspareunia				
none	37	(52)	42	(58)

Table 2 SF 36 Health Survey Questionnaire: - mean baseline scores and change in score at five-year follow up.

Scores range from 0 → 100 (worst → best) Follow-up statistical comparisons between trial groups are for change in score

Asterisks denote significant changes in score from the baseline (*p < 0.05, **p <0.01, ***p <0.001)

	Medical n = 70		TCRE n = 73				
	mean	SD	mean	SD	difference	P value	95% C.I.
Short Form 36 - baseline scores (S.D.)							
physical functioning	77.8	(21.78)	81.38	(19.57)	-3.58	0.31	-10.62 to 3.4
social functioning	69.7	(21.4)	69.73	(23.71)	-0.03	0.99	-7.73 to 7.67
role - physical	55.22	(39.06)	53.26	(38.67)	1.96	0.77	-11.24 to 15.2
role - emotional	59.2	(42.96)	52.24	(43.39)	6.96	0.23	-5.69 to 23.61
mental health	58.12	(17.70)	58.03	(18.62)	0.09	0.98	-6.1 to 6.28
energy/fatigue	40.15	(17.05)	40.29	(19.59)	-0.14	0.97	-6.4 to 6.13
pain	55.72	(23.65)	59.74	(24.93)	-4.02	0.34	-12.3 to 4.22
general health	69.7	(20.52)	65.31	(20.46)	4.39	0.22	-2.59 to 11.37
Short form 36 - change in score (S.D.)							
physical functioning	1.06	(23.81)	7.57**	(16.39)	-6.01	0.1	-14.4 to 1.3
social functioning	2.96	(27.22)	10.14**	(24.49)	-7.18	0.1	-16.0 to 1.6
role - physical	15.14**	(39.77)	31.62***	(33.15)	-16.48	0.06	-33.8 to 0.9
role - emotional	14.35*	(40.61)	33.81***	(34.11)	-19.46	0.02	-36.3 to –2.5
mental health	3.62	(18.21)	13.26***	(16.94)	-9.64	0.01	-16.9 to –2.4
energy/fatigue	10.62***	(18.79)	17.31***	(22.35)	-6.69	0.07	-13.9 to 0.5
pain	11.98***	(23.66)	14.81***	(25.35)	-2.83	0.6	-13.4 to 7.7
general health	-3.88	(20.13)	6.79*	(23.10)	-10.67	0.01	-18.9 to –2.4

Table 3 **Menstrual status and symptoms at five year follow-up. Values are numbers of women (percentages), unless stated otherwise.**

	Medical		T.C.R.E.		difference	95% C.I. for difference	P value
Menstrual status							
no bleeding or very light	47/71	(66)	61/73	(84)	-22%	-31% to -4%	0.02
lighter	15/71	(21)	9/73	(12)	9%	-3 to 21%	0.18
unchanged or heavier	9/71	(13)	3/73	(4)	9%	-1% to 18%	0.07
Duration of bleed							
amenorrhoea	41/71	(58)	47/73	(64)	-6%	-26% to 5%	
1 - 3 days	4/71	(6)	10/73	(14)	-8%	-18 to 1.5%	0.13
3 - 7 days	24/71	(34)	14/73	(19)	15%	0.3% to 29%	
>7 days	2/71	(3)	2/73	(3)	0%	-5% to 5%	
Days heavy bleeding – median (75 centile)	0.0***	(2.0)	0.0***	(0)			0.02
Bleeding score - median -(75 centile)	0.0***	(8.75)	0.0***	(3.0)			0.30
Pain score - median -(75 centile)	0.0***	(6.25)	0.0***	(1.0)			0.17
Dysmenorrhoea - same or worse	13/71	(18)	6/73	(8)	7%	-1% to 21%	0.35
Dyspareunia - none	56/69**	(79)	54/70**	(77)	2%	-9% to 18%	0.89
Premenstrual symptoms							
breast discomfort	30/67***	(45)	36/71***	(51)	-6%	-23% to 11%	0.5
bloating	44/67	(66)	47/71***	(66)	0%	-16% to 15%	0.54
irritability	32/67**	(48)	38/71**	(54)	-6%	-22% to 11%	0.61
headaches	23/67***	(34)	26/71***	(37)	-3%	-18% to14%	0.86
depression	29/67	(43)	24/71**	(34)	9%	-7% to 26%	0.3

Asterisks denote changes from baseline (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$)

Difference in means or proportions(%). 95% C.I. for difference = 95% confidence intervals for difference in means or proportions(%).

Table 4 **Patient satisfaction, effectiveness and acceptability of treatment, and recommended treatment.**
Values are numbers of women (percentages) unless stated otherwise.

	Medical		T.C.R.E		difference	95% C.I. for difference	P value
Totally satisfied with treatment	27/69	(39)	44/72	(61)	-21%	-37% to –4%	0.01
Generally satisfied with treatment	22/69	(32)	14/72	(20)	8%	-2% to 27%	0.14
Cure or acceptable improvement in symptoms	52/69	(75)	61/71	(86)	-11%	-23% to 2%	0.26
Treatment acceptable	64/70	(91)	65/70	(93)	-2%	-10% to 7%	0.75
What treatment would you recommend to a friend?							
none	9/70	(13)	2/72	(3)			
medical	**14/70**	(20)	3/72	(4)			
TCRE	36/70	(51)	**57/72**	(79)	-59%	-73% to –45%	0.001
hysterectomy	11/70	(16)	10/72	(14)			

95% C.I. for difference = 95% confidence intervals for difference in proportions(%)

comparison of recommended treatments made between initially allocated treatment groups (**highlighted**)

Figure 1 - Trial profile

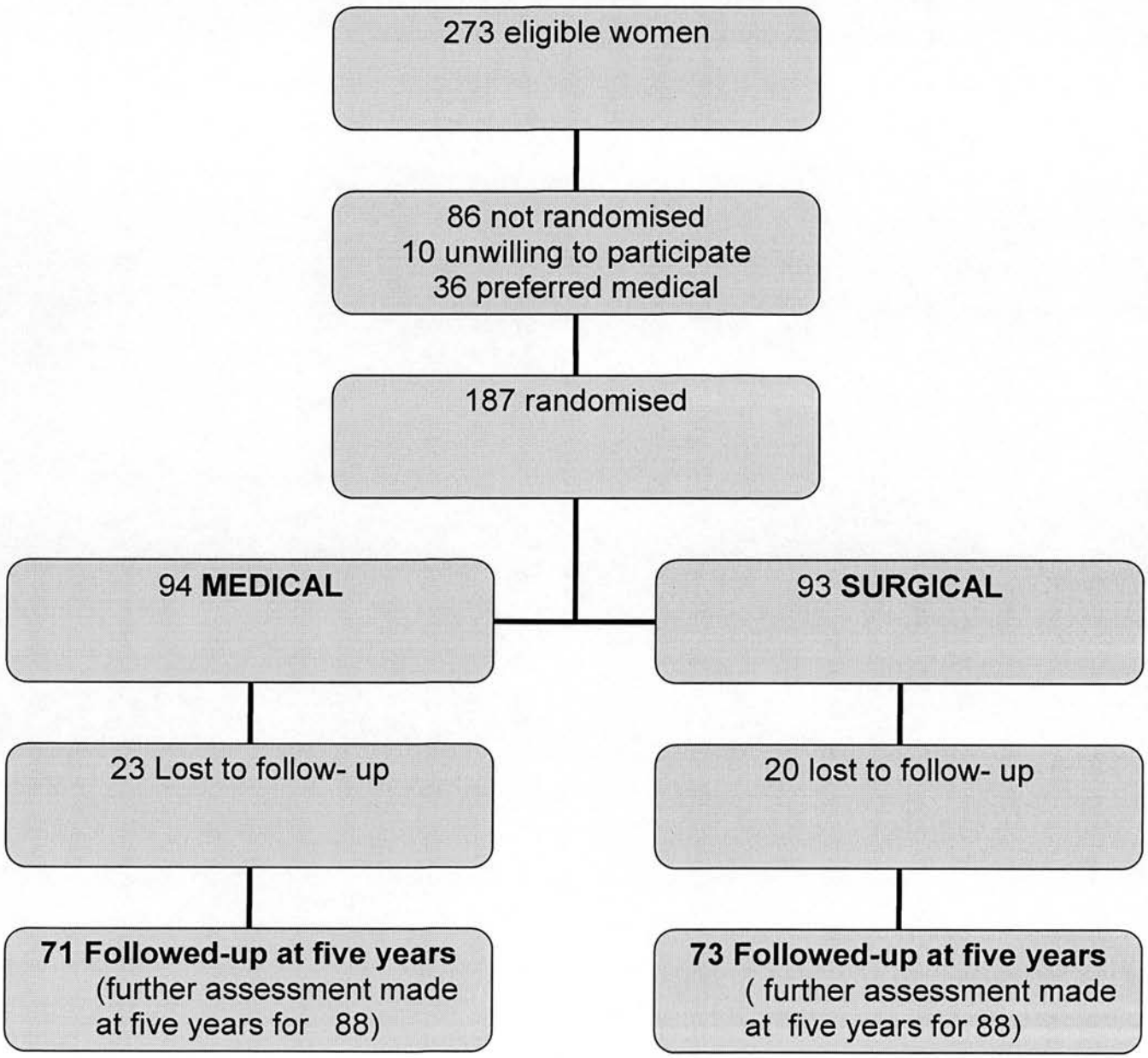


fig. 2. Operative rate anually to five years (actual numbers of patients)

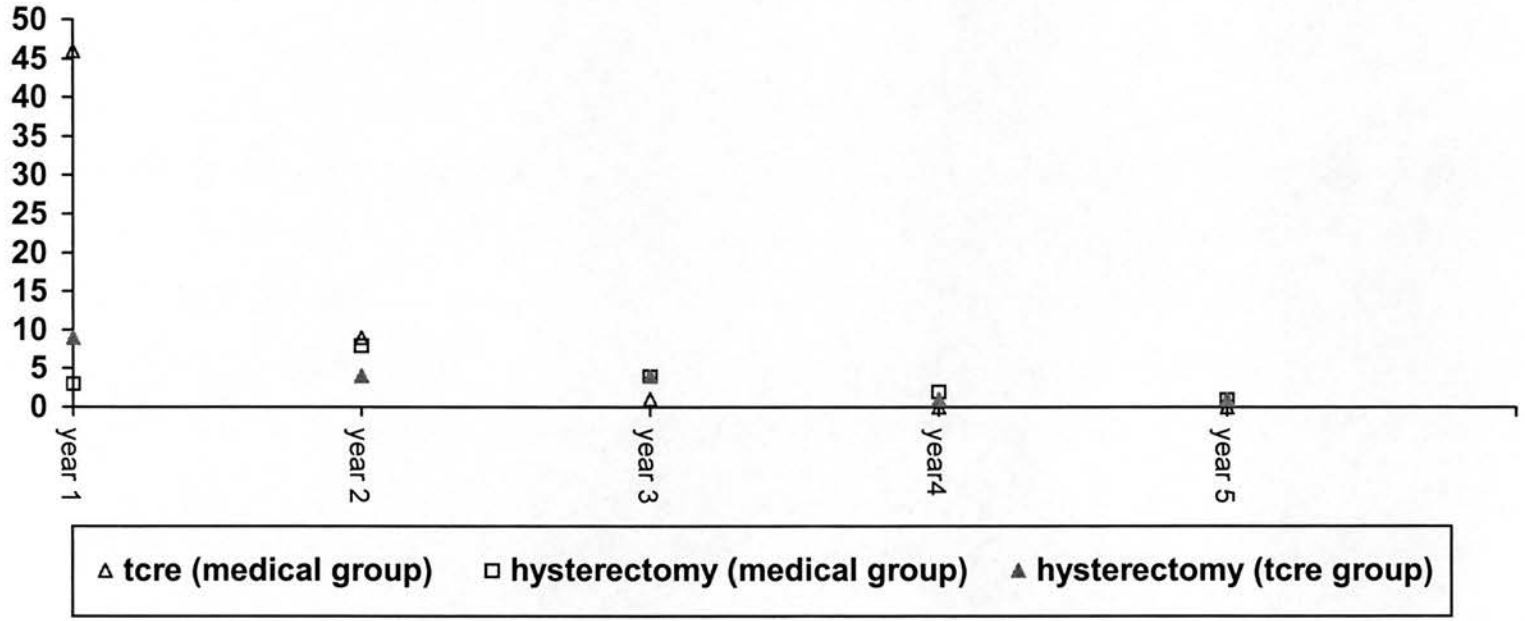
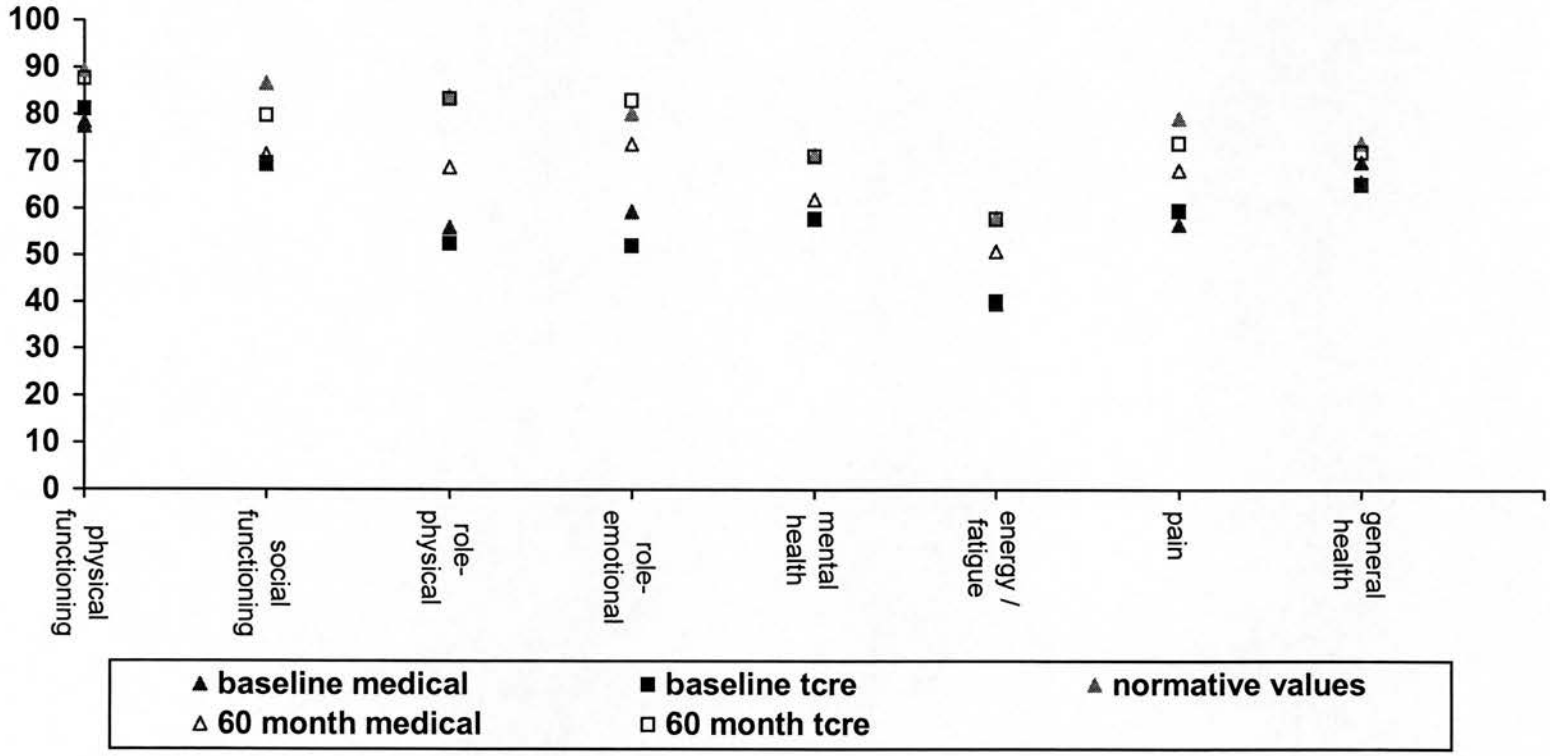


fig. 3. Short Form 36 scores



Chapter 3

A Randomised Multicentre trial of Microwave Endometrial Ablation versus Rollerball Endometrial Ablation in the treatment of menorrhagia.

3.1 Introduction

Excessive menstrual bleeding (menorrhagia) is a common complaint for which each year 1 in 20 of women aged 30 –49 consults their general practitioner. Menorrhagia has been defined from population based data as a blood loss of over 80 mls / cycle and is cited as the reason for over one third of the 600,000 hysterectomies per annum performed in the US[236]. In England approximately 52,000 hysterectomies and 16,000 endometrial ablations are performed per annum in the public sector, almost half of these for heavy menstrual bleeding [323]. Whilst efficacious hysterectomy is associated with significant morbidity, costs and prolonged recovery [197;214;324;325].

Endometrial Ablation emerged in the 1980's with first Endometrial Laser Ablation pioneered by Goldrath in 1981[170] in the United States (US) and introduced into the UK in 1986 by Davies [171]and with the introduction of TCRE by Magos in 1989 [172].These first generation technologies established themselves as an effective and safe alternative to hysterectomy [173;188;189;191;210]. It offered significantly faster recovery, shorter hospital stays and fewer complications. In the hierarchy of treatments it proved superior over the long term to medical treatments and only slightly inferior to hysterectomy[15;19;181;182;189;191]. First generation Ablative techniques (combined loop resection and rollerball ablation, rollerball endometrial ablation and endometrial laser ablation) gave good results but were technically difficult to perform, with a long

learning curve and new potentially serious procedure related complications such as fluid overload[173;326;327].

In the 1990's second generation techniques emerged that offered simple to learn, quick procedures that avoided many first generation complications.

Microwave Endometrial Ablation (Microsulis, Waterlooville, Hampshire, UK) a second generation device, was first developed in Bath, England in 1993. It has a sound evidence base. MEA has been compared in an RCT to the gold standard of TCRE (combined loop resection and rollerball ablation) with follow up data to five years[223;299;328]. Adequately powered methodologically sound RCT evidence of its suitability under local anaesthesia is compelling and is expanding[329;330].

We undertook a multicentre international investigation of MEA versus Rollerball Endometrial Ablation (RBEA) in the context of a phase III clinical trial.

3.2 Patients and Methods

3.2.1Study Design

Between April 2000 and September 2001, 322 women were enrolled in a clinical trial comparing microwave endometrial ablation (MEA) with Rollerball Endometrial Ablation (RBEA). Eight investigation sites were involved - 5 in the U.S, 2 in Canada and 1 UK site (Table 1). All investigators were gynaecological surgeons who had previous extensive experience of rollerball ablation and had been trained in MEA. A MEA preceptor supervised all the early MEA treatments to monitor training issues ensuring a standardised approve technique was utilised by all. The institutional review board or local area ethics committee at each site approved the study. All patients were fully counselled and gave written informed consent to participate in the trial prior to screening and treatment. The study was not blinded. For the centres in the United States the trial was performed under an investigational device exemption approved by the Food and Drug Administration and was a phase III clinical trial.

Women over 30 years were randomised only once they had satisfied the inclusion/ exclusion criteria of the study (see 3.2.4 Eligibility). Women were randomised in a 2:1 basis to MEA: REA. The reason for this unbalanced allocation was to maximise the observations of the novel therapy (MEA) .Randomisation was computer generated random numbers accessed via the internet, stratification of women above and below 40 years was performed as this was felt to be a potential confounding factor with some trials reporting better outcome in the over 40 year old age group[210;331].

The primary end point was the reduction of pictorial blood loss assessment chart (PBLAC) scores to less than or equal to 75 at 12 months post procedure (PBLAC $\leq$ 75 being equivalent to normal period or eumenorrhoea). Secondary outcome measures were amenorrhoea rate, satisfaction, acceptability, quality of life scores (SF-36) , duration of procedure, anaesthesia, device related complications, adverse incidents and dysmenorrhoea.

After eligibility screening and consent all patients received a single injection of endometrial preparation (leuprolide acetate depot [Lupron, Wyeth Pharmaceuticals, UK], 3.75 mgms i.m.) 3-5 weeks prior to surgery. This preparation was chosen as it is the most commonly utilised GnRH analogue in North America.

Post procedure PBLAC diaries were maintained prospectively each month for 12 months. Post procedure data collection including patient questionnaires, adverse events and quality of life evaluations utilising Short Form 36 (SF -36 [332]) were completed at 1 day, 14 days, 6 and 12 months. Patients were telephoned at 24 hours to assess symptomatology and document any adverse events from the procedure, face to face reviews with the research fellow were made at two weeks, 3, 6 and twelve months.

The incidence of further surgery was recorded. There were two hysterectomies (one in each arm). In the MEA group one patient required a total abdominal hysterectomy and right salping-oopherectomy for a benign ovarian mass, in the RBEA group there was one hysterectomy for menstrual dissatisfaction despite PBLAC scores of 20. One pregnancy occurred in the RBEA arm and subsequently miscarried.

3.2.2 Statistics

The primary outcome measure was success of treatment as defined as reduction of the PBLAC scores to less than 75 consistent with eumenorrhoea. Secondary outcome measures were amenorrhoea rate, satisfaction, acceptability, quality of life scores (SF-36) , duration of procedure, anaesthesia, device related complications, adverse incidents and dysmenorrhoea.

The sample size required was based on the hypothesis that the two treatments of MEA and RBEA would achieve equivalent results in the primary outcome measure based on an estimate of 84.3% patients reporting a PBLAC of less than 75 at the 12 month follow-up in the RBEA group. The planned sample size of 310 yielded a power of 80% to detect equivalence at the 5% significance level.

Data based on intention to treat analysis (where all non responders or missing data is recorded as a treatment failure) and evaluable population analysis (where only the data recorded by responders is utilised) was recorded.

SPSS statistical software was used to create the database and perform statistical analysis. Fishers Exact test was used to analyse nominal data. T tests were used to analyse continuous variables that were normally distributed. Kruskal- Wallis tests were used to analyse differences between the groups in apportionment across ordered PBLAC outcome categories. 95% confidence intervals were used where appropriate.

3.2.3 Procedure

Patients were treated in their randomised groups.

Anaesthetic use (local [plus or minus sedation] , regional , general anaesthesia) was left up to the discretion of the operator, anaesthetist and the patients preference. All women received Lupron (3.75 mg leuoprelin acetate) endometrial preparation 3 -5 weeks pre-operatively.

MEA was performed with the utilisation of pre-operative hysteroscopy in what is now the recommended fashion. The cavity was sounded, the cervix dilated to 9mm diameter and carbon dioxide hysteroscopy was performed to confirm the cavity as intact and exclude false passage formation and / or uterine wall trauma. Carbon Dioxide is preferable to saline as the distension medium as it prevents the potential cornual sparing effect reported with saline hysteroscopy.[301] The cavity length was rechecked and the MEA probe (8.5 mm) in diameter was inserted. The treatment was commenced only if the probe insertion depth equalled the established uterine cavity depth.

The initial temperature rise (recorded from the thermocouple at the tip of the probe and displayed on screen) to 60 degrees is effectively gated. If as previously discussed in Chapter 4 the profile moves out of the gated zone the device is inactivated, treatment terminated and hysteroscopy suggested.

Once past the initial 60 degree point (approximately 5 seconds into treatment) the probe is moved gently side to side to create a fundal warming effect. Once the 70 -80 degree range is achieved the probe is gently displaced laterally to commence treatment of each cornual region in turn (no more than 5 seconds). The probe is then gently withdrawn in 0.5cm increments treating the walls of the uterus using a gentle side to side motion whilst keeping the temperature display in the therapeutic range (70 – 80 degrees Celsius). All operators in the trial were experienced with MEA and all initial treatments were supervised by a Microsulis preceptor to ensure uniformity of treatment and exclude any training issues.

The RBEA treatments were performed in a standard fashion commencing treatment at the cornual regions, extending over the fundal region and then treating the anterior, posterior and lateral walls. Patients in the Rollerball Arm with fibroids / polyps were resected first with a resection loop then rollerball performed. Urological Glycine (1.5%) was used as the distension media.

3.2.4 Eligibility

Patients were eligible for the trial if they were over 30 years of age, had completed their family, failed or not tolerated standard medical treatment for heavy menstrual bleeding and had demonstrable menorrhagia. Menstrual Blood loss was evaluated with PBLAC charts. Scores greater than 185 correlate to menorrhagia using the charts designed by Higham et al and modified by Janssen et al.[23;333] In Janssen's study using a score of 185 as the cutoff point, the predictive values of positive and negative tests for menorrhagia are high, 85.9 and 84.8%, respectively. All women eligible for the trial had their PBLAC score measured prospectively prior to randomisation (over one cycle if they previously received treatment for menorrhagia or as an average of 3 cycles if not previously treated). Standardised sanitary ware was utilised and issued to all potential trial participants to prevent errors in the scoring of the PBLAC diaries that can occur if patients utilise their own preferred sanitary ware.

All women had a transvaginal ultrasound plus or minus hysteroscopy to evaluate the uterine cavity regularity. Non obstructing fibroids and / or polyps up to 3 cm were included. All women had demonstrable uterine wall thickness of 8 mm or more. Women with previous endometrial ablation, previous classical section or myomectomy were excluded. All women were required to have a normal endometrial biopsy (within the last 6 months) with cavity lengths of 6 – 14 cm inclusive. A recent (within 6 months) normal cervical screening smear was also required. All women were required to have an internal examination, genital cultures for chlamydia and gonorrhoea and a negative pregnancy test. Follicle Stimulating Hormone (FSH) level of <30 IU/ l was utilised to exclude peri –menopausal women. Women with untreated cervical dsyplasia, untreated pelvic infection, coagulation defects, a previous history of gynaecological malignancy in the last 5 years and intrauterine contraceptive device wearers were excluded. Patients were willing to accept either treatment allocation and were not blinded to their allocation.

3.3 Results

A total of 322 women were randomised in the study (see Fig 1). 215 were randomised to MEA and 107 to REA.

Six patients did not undergo MEA as they proved unsuitable for the procedure at the time of surgery. Three women had obstructing sub-mucosal fibroids that had been misdiagnosed on pre-randomisation ultrasound / hysteroscopy, one woman had cervical stenosis and two suffered perforation during dilation.
One woman on the Rollerball group did not receive treatment as she had an obstructing fibroid preventing access to the cavity.

3.3.1 Baseline Characteristics

The groups did not differ in baseline characteristics of age (note randomisation was stratified into age greater or less than 40), body mass index, PBLAC scores at entry, uterine cavity length, race, dysmenorrhoea and the presence of fibroids (see table 2). Of note the Aberdeen cohort was 100% Caucasian, reflecting the limited ethnical diversity in the population. Regarding the age stratification (less than or greater than 40 years), 44% in the MEA and 41% in the REA groups were patients under 40 years.

3.3.2 Clinical Outcomes

In the ITT analysis of success (as defined by PBLAC < 75) at twelve months there was no statistically significant difference between the two groups. 187(87.0%) in the MEA group and 89 (83.2%) in the REA group recorded treatment success (see Table 3). There was no statistical significant difference in the numbers recording amenorrhoea (see table 2), 55.3% in the MEA group and 45.8% in the REA group recorded amenorrhoea at 12 months.

A high Body Mass Index (BMI) has been implicated in improved outcomes. [188] In this trial there was a significant difference in outcomes in terms of success seen when the data was stratified by BMI < 30 kg/m^2 and BMI ≥ 30 kg/m^2 (see table 4).

1.3.3 Fibroids

The effect of the presence or absence of non obstructing fibroids $\leq$ 3cms was assessed. In those with fibroids present there was a higher degree of reported success in the REA group but this was not significant, also there was no significant difference in the recorded amenorrhoea rates between the groups. The absence of fibroids was associated with improved outcomes in terms of amenorrhoea rates and success for both treatment groups (see table 5).

1.3.4 Anaesthesia

Study data pertaining to type of anaesthesia (a non randomised outcome measure) yielded a significantly lower number of MEA versus REA patients receiving general anaesthesia, 45% and 78% respectively ($p< 0.01$). Of note the Aberdeen site utilised only general anaesthesia due to a misunderstanding of protocol. Mean treatment times ($\pm$ 2 standard deviations) were significantly shorter for the MEA group at 3.45 $\pm$ 1.02 minutes versus 20.22 $\pm$ 15.60 minutes for the REA group.

1.3.5 Quality of Life

Quality of life was measured utilising SF 36 at trial entry and to 12 months post treatment were analysed in physical component scores and mental component scales. Pre-treatment physical component scales for the MEA group were 47.1$\pm$ 9.22, and 54.1$\pm$ 6.6 post-treatment. Pre-treatment physical component scales were 46.5 $\pm$ 8.1 for the REA group and 53.6 $\pm$6.9 post-treatment.

Pre-treatment mental component scales for the MEA group were 46.5 + 11.5 and 52.2 + 9.1 post treatment. Pre-treatment mental component scales for the REA group were 46.6 + 11.4 and 51.5 $\pm$ 9.7 post treatment.

Pre-treatment dysmenorrhoea was reported by 81.8% (176 / 215) in the MEA group and by 30.6% (66 /215) at 12 months. In the REA arm 80.4% (80 / 107) reported dysmenorrhoea pre-operatively whilst 34% (36 / 107) reported it post –operatively.

1.3.6 Adverse Events

In keeping with the Phase III trial nature of the study adverse events were closely monitored. All post operative adverse events were recorded by the women in the study and assessed at 24 hrs (see table 6). There was a significantly higher incidence of post operative vomiting and uterine cramping noted after MEA. There were no significant or serious post operative events seen in either arm. There were no equipment failures or device related adverse events. Four cervical lacerations (two in each group), one cervical stenosis in the MEA arm, two cervical perforations pre- treatment in the MEA arm.

There were six cases of endometritis in the MEA arm, with none recorded in the REA arm. All cases responded to antibiotic therapy. By one year there was no significant difference in the incidence of adverse events reported in either trial arm. There was a trend to higher reported uterine cramps in the MEA group versus the REA group (9% and 3% respectively).

3.4 Discussion

As a technique MEA is easier and faster to learn than hysteroscopic techniques such as REA and the gold standard of TCRE. It also requires considerably less technical skill. The vast majority of gynaecologist after suitable training will be able to achieve consistent results after 3 cases. [334] In comparison approximately ten times as many cases are required before competency is achieved in the hysteroscopic surgical techniques.

This study demonstrates a number of features of MEA with regards to treatment times, anaesthesia, menstrual outcomes and its efficacy with non – obstruction fibroids (up to 3cms) . The significantly shorter duration of treatment with MEA when compared to REA / TCRE is well demonstrated and has been confirmed in previous studies. [299] It is also notable that the technique was able to perform under a combination of local anaesthesia and intravenous sedation in a significantly greater percentage than was the case for REA (62% of cases versus 18% respectively). The Aberdeen site deviated on anaesthetic protocol due to a misunderstanding that all patients were to be treated under general anaesthesia that was only identified at the data collection stage. This contributes to the general data on MEA and lends support to its use as an outpatient technique, however as this was left to individual patients and surgeons discretion its is prone to biases that reduce the generalisability of these findings back to a general population.

Eumenorrhoea, Hypomenorrhoea or Amenorrhoea was achieved by 87% in the MEA group by intention to treat analysis. Treatment success as defined as a PBLAC score of 75 or less was greater for MEA than REA, but not significantly so. Likewise amenorrhoea rates were similarly higher in the MEA group but not significantly so.

Certain sub groups were studied that previous research had shown affects with respect to outcome – those forty years of age and over, those with a BMI over 30 kg/m^2 and the presence of fibroids.

There was no significant difference seen in levels of success between those stratified by age in either the MEA or REA groups. The previously identified effect of improved outcome with age over 40 years [210] was not demonstrated in this trial.

Regarding the effect of BMI on treatment success rates there was a significantly greater effect seen in the MEA group in those with a BMI of 30 kg / m^2 or greater, confirming previous work by Gannon.

The effect of the presence of fibroids was investigated as this is a known adverse prognostic feature for both first and second generation ablative technologies.[174;252;299;335] Many second generation endometrial ablative techniques require a small (10 cm or less)

regular cavity. For others there is little data on the efficacy of the treatment in the presence of fibroids. To increase the generalisability of the study fibroids up to and including 3cm that and non -obstructing were included with the REA group albeit that hey were augmented by a wire loop excision of the fibroid, a treatment that many would argue would be the gold standard for hysteroscopic treatment of intra-cavity fibroids. The analysis outlined in the previous chapter revealed MEA when compared to REA as having a similar (68.3% versus 76.7%) success rate and a higher (but not significantly so) amenorrhoea rate with 46.3% in the MEA (fibroids present) arm reporting amenorrhoea at 12 months. Thus from the trial data this suggest that MEA has comparable and acceptable efficacy to combined REA and wire loop resection in the treatment of intra-cavity non- obstructing fibroids. As identified in previous studies the absence of fibroids was associated with higher reported success rates and amenorrhoea rates in both arms.

Race was also assessed and found not to effect outcome. The Aberdeen site was 100% Caucasian, reflecting the relative lack of racial diversity in the population in the North East of Scotland versus that seen in the North American sites.

With regards to satisfaction, a key outcome measure in all endometrial ablation trials comparable recorded levels of satisfaction were recorded in the MEA group and REA group.

In keeping with the effect on QOL scores reported in other ablation studies [181;223;299] there was a significant improvement in the SF 36 score for the physical and mental scales for both MEA and REA at one year follow-up but no significant difference between the techniques.

A previous concern with all new generation technologies is the reliability of the device. Many studies including early MEA trials reported equipment failures. The Cochrane Endometrial Ablation review group highlighted this as an area of interest and encouraged all new device manufacturers to report such technical failures / problems. There were no equipment failures in this trial. This represent a general improvement in the robustness of the technology seen in the MEA (Version 2) and borne out in the more

recent MEA trial reported in the next chapter where again there were no technical failures.

The multicentre, international RCT design increases generalisability, also the inclusion and exclusion criteria of this trial (including a range of cavity lengths and the presence of fibroids) was not restrictive again improving generalisability.

The fact that the trial was performed under the auspices of an FDA Phase III trial deserves further discussion. The trial was paid for by Microsulis America PLC and as previously discussed all trial funded by an interested party are subject to bias. That said the regulatory function of the FDA, including data checks; site visits and interviews provide protection against the undesirable effects of commercial pressure. The potential for at best the introduction of bias and at worst scientific fraud entering into the evaluation of a technology is always there when a product is applying for approval prior to its launch into the most valuable free market in the world. In keeping with research practices in North American these sites paid their patients to attend the follow-ups, covering all travel and out of pocket expenses. In keeping with UK scientific regulations none of the UK enrolled patients received any financial incentive. A financial incentive may create an atmosphere of bias with the trial participants, however as both arms of the trial were being paid this may not affect the outcomes.

3.5 Conclusion

This study further contributes to the already solid evidence base of MEA. The MEA has already been compared in a RCT with the gold standard TCRE and the data from this trial. In terms of clinical outcome MEA in this study compares favourably with the REA. The comparison to REA is valid as the population was predominately North American and REA is the predominant ablation technique in North America.

MEA offers rapid treatment times, the possibility of local anaesthetic treatments and high patient satisfaction. The low rates of further surgery at one year are also

encouraging. The conclusion from this study is that treatment with MEA gives results as good as and in many cases better than those seen in the REA arm. The technology is dependable, easily learnt as a technique and within the confines of this trial would appear safe.

g 1 Trial Design

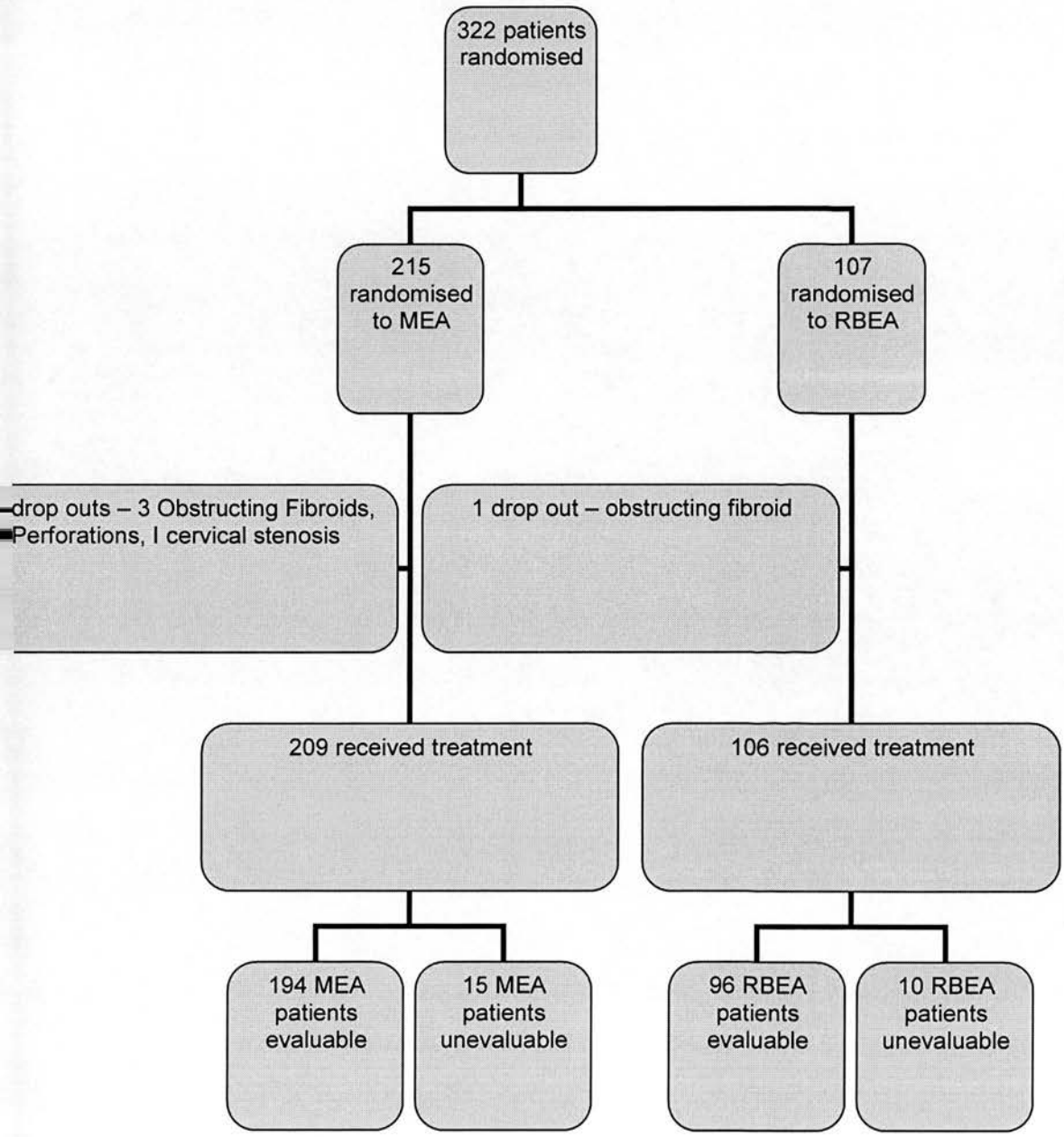


Table 1 Contributors and Departments

Investigator	Site	Enrolled		
Ted Anderson, MD Bryan Kurtz, MD	Clinical Research Associates Nashville, TN	29		
Jay Cooper, MD Micah Harris, MD	Women's Health Research Phoenix, AZ	60		
Claude Fortin, MD	LaSalle Hospital LaSalle, Quebec	64		
Gregory Fossum, MD Carl Della Badia, MD Ben Gocial, MD Jay Goldberg, MD	Thomas Jefferson University Philadelphia, PA	34		
Beverly Love, MD Roosevelt McCorvey, MD	Women's Wellness Center Montgomery, AL	13		
Kevin Cooper, MD Stuart Jack, MB ChB	Aberdeen Royal Infirmary Foresterhill Aberdeen, Scotland	39		
Philippe Laberge, MD Pierre Blanchette, MD	CHUQ Pavilion CHUL Sainte-Foy, Quebec	56		
Linda Bradley, MD	Cleveland Clinic Foundation Cleveland, OH	27		
	Totals	**322**		

Table 2 Baseline Patient Characteristics

Characteristic	MEA		REA		p
	Mean	SD	Mean	SD	
Age (years)	40.50	4.60	40.90	4.60	0.48
Body Mass Index (BMI)	28.00	7.10	27.00	6.60	0.25
PBLAC Scores	451.80	356.60	524.60	429.50	0.11
Uterine Cavity (cm)	8.09	0.98	8.14	0.77	0.61
	N	%	N	%	
Race					0.92
Black	22.0	10.2	12.0	11.2	
Caucasian	187.0	87.0	93.0	86.9	
Other	6.0	2.8	2.0	1.9	
Dysmenorrhoea					0.76
Present	176.0	81.9	86.0	80.4	
Absent	39.0	18.1	21.0	19.6	
Myomas					0.09
Present	41.0	19.1	30.0	28.0	
Absent	174.0	80.9	77.0	72.0	

SD = Standard Deviation

p = statistical significance (0.05)

Table 3 Menstrual Outcomes

Menstrual Outcome	N	% (95% CI)	p
Success			0.40
MEA	187	87.0 (81.7 – 91.2)	
REA	89	83.2 (74.7 – 89.7)	
Amenorrhoea			0.12
MEA	119	55.3 (48.4-62.1)	
REA	49	45.8 (36.1-55.7)	

p = statistical significance (0.05)

Table 4 Effect of BMI on Success

BMI (kg / m^2)	N	% (95% CI)	p
< 30kg / m^2			0.82
MEA	193	89.7 (83.3 -94.3)	
REA	94	88.5 (79.2-94.6)	
≥ 30kg / m^2			0.05
MEA	184	85.3 (74.6-92.7)	
REA	71	66.7 (46.0-83.5)	

p = statistical significance (0.05)

Table 5 Effect of Fibroids on Success / Amenorrhoea (ITT Analysis)

Fibroids – Effect on Success	**N**	**% (95% CI)**	**p**
Fibroid Present			0.59
MEA (n=41)	28	68.3 (51.9-81.9)	
REA (n= 30)	23	76.7 (57.7-90.1)	
Fibroid Absent			0.18
MEA (n=174)	159	91.4 (86.2-95.1)	
REA (n= 77)	66	85.7 (75.9-92.6)	
Fibroid – Effect on Amenorrhoea			
Fibroid Present			0.33
MEA (n=41)	24	58.5 (49.8-64.9)	
REA (n= 30)	15	50.0 (39.0- 62.2)	
Fibroid Absent			0.34
MEA (n=174)	81	46.5 (30.7-62.6)	
REA (n= 77)	26	33.3 (17.3-52.8)	

Table 6 Adverse Events at 24 hrs

Adverse Event	MEA		REA		p
	n	%	n	%	
Chills	19	8.8	7	6.5	0.52
Dysuria	17	7.9	11	10.2	0.53
Fever	2	0.9	0	0.0	0.55
Headache	6	2.8	4	3.7	0.74
Nausea	49	22.6	18	16.6	0.25
Vomiting	29	13.4	4	3.7	0.006
Urinary Tract Infection	1	0.5	1	0.9	1.00
Vaginal Discharge Infection	1	0.5	0	0.0	1.00
Uterine Cramping	155	71.8	64	59.3	0.032
Abdominal Tenderness	11	5.1	9	8.3	0.33
Bloating	15	6.9	9	8.3	0.66

Chapter 4

Microwave endometrial ablation without endometrial preparation in the outpatient setting: patient acceptability, treatment outcome and costs. A randomised controlled trial.

4.1 Introduction

Microwave endometrial ablation (MEA^{TM}) is a safe and effective conservative surgical treatment for the treatment of excessive menstrual bleeding. [223;299;303;304;308;329] Unlike traditional first generation endometrial ablative techniques MEA can be quickly learnt, can treat most uterine cavities, and has been shown to be acceptable under local anaesthetic. [299;304;336]

Traditionally, endometrial ablations are performed after thinning the endometrium, usually with GnRH analogues or Danazol. This hormonal preparation results in better visibility, reduces intra operative fluid absorption, shortens operative times and improves outcomes. [337;338] These findings apply to first generation hysteroscopic based ablative techniques such as rollerball and laser ablation, and may not apply to microwave ablation. GnRH analogues increase cervical resistance, making dilatation more difficult and potentially increasing the risk of cervical injury, uterine perforation and false passage formation. [339] Danazol has therefore been used as endometrial preparation for women undergoing MEA^{TM} under local anaesthetic, to avoid the discomfort associated with dilatation against increased cervical resistance. [340] Although endometrial preparation allows predictable scheduling of operations four to six weeks from commencement, treatment with Danazol or GnRH analogues is associated with unpleasant side effects, and is expensive.

Since microwave endometrial ablation requires neither cavity visualisation during the treatment phase nor a fluid media to distend and irrigate the uterine cavity [303;304] endometrial preparation may not be necessary.

The aim of this study was to assess patient satisfaction with, and acceptability of MEA under local anaesthesia performed in an operating theatre, after five weeks of endometrial preparation, compared to MEA on an unprepared endometrium performed in a genuine outpatient setting.

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4.2 Patients and Methods

4.2.1 Participants

The study was submitted and approved by the local area ethics committee. Primary outcome measures were patient acceptability and satisfaction. Secondary outcome measures were menstrual outcome and cost both to the health service and the patient and their families (non-health service costs).

Eligible patients were those complaining of excessive menstrual loss who would consider Microwave Endometrial Ablation under local anaesthesia and who fulfilled the pragmatic inclusion criteria – normal endometrial pathology, finished family, uterine size of 12 weeks or less. Non-obstructing submucous fibroids up to 3cm in size which were included. To increase the generalisability of the study and in keeping with its pragmatic nature patients were not routinely hysteroscoped or scanned prior to recruitment. Patients were recruited from the dedicated Menstrual Clinic, General Gynaecology clinics and surrounding peripheral clinics of the Aberdeen Royal Infirmary.

Patients were counselled fully regarding the procedure, were given written information on MEA procedure and the study. Fully informed written consent was gained. Patients were randomised to either genuine outpatient treatment in the postmenstrual phase (

performed in the treatment room of the gynaecological ward) or to standard treatment after endometrial preparation (Danazol 200 mgs / bd. for 4-5weeks or one Zoladex 3.6mgms s/c 5 weeks pre-op) in the day case theatre. All MEA procedures were performed under local anaesthesia with or without mild sedation. Sedations was administered by the anaesthetist in those treated in day case theatre or by the treating doctor in the outpatient treated arm. Rescue intravenous analgesia was used if required. Patients who failed to tolerate the local anaesthesia regime were offered conversion to general anaesthesia in the day case theatre arm or rescheduling treatment under general anaesthesia in day case theatre at a later date with endometrial preparation in the outpatient arm.

4.2.2 Procedures

Patients were randomised in a ratio of 1:1. Computer generated balanced random number blocks were used and the sealed, opaque, sequentially numbered randomisation envelopes kept at a separate site. Randomisation was gained by the research fellow telephoning the gynaecology secretary who opened the next numbered opaque envelope. Patients' randomised to post menstrual treatment telephoned the research fellow on the first day of their period to arrange treatment appointments. These post menstrual phase treatments were performed after naturally occurring menses, no hormonal manipulation was used. Patients were treated in days 3-10 of their cycle. Day 1- 3 of a woman's cycle are commonly the heaviest and represent the days when the majority of the endometrium is shed, treatment was not performed in those days. After day 10 the endometrial thickness commonly exceeds 10mm which could compromise therapeutic effect. [301;303]

Patients completed pre-operative questionnaires to obtain baseline menstrual details, quality of life parameters (Short Form 12) [341] and an assessment of anxiety and depression (Hospital Anxiety and Depression Score). [342] Women's menstrual pain and blood loss was assessed using a five-point scale of the severity of their symptoms (1-mild, 5 severe). The scale gave a score from zero to fifty for bleeding and pain.

Operative details including endometrial thickness at operation measured by transvaginal ultrasound scan were recorded. Procedure related pain was measured using the modified McGill Pain Questionnaire. [343]

Clinical questionnaires were sent at two weeks. For women who had received the hormone preparation treatment costing questionnaires were completed at treatment and 4 weeks to collect data on health service and non-health service resource use. Acceptability of the procedure was assessed using a six-point Likert type scale and on a 10cm visual analogue scale (0cm = totally acceptable, 10cm = totally unacceptable).

Patients received a 100mg Voltarol suppository 1 hour prior to treatment (patients unsuitable for NSAID received 1gm of Paracetamol). A venflon was sited prior to commencing the treatment. Patients were offered i.v. sedation with Midazolam (2-4mgs i.v. maximum), either from the outset or at their request intra –operatively. If intraoperative analgesia was required, i.v. Fentanyl was used (25-50mcgms, i.v. maximum). Patient's oxygen saturation and heart rate were monitored during the procedure.

Post menstrual phase outpatient treatments were performed in the treatment room of Ward 42 of Aberdeen Royal Infirmary. If required beds were available for recovery if the patient suffered from nausea or pain. Treatment after endometrial preparation were performed in the Day Case Theatre of Aberdeen Royal Infirmary on scheduled elective lists.

All patients had a member of the nursing staff with them throughout the procedure for reassurance and to provide 'verbal anaesthesia'. All received a four quadrant cervical block using a 2.2ml ampoule of Citanest 3% , (3% Prilocaine with Felypressin 2.2mls)

to each quadrant and a transvaginal ultrasound scan performed to establish endometrial thickness. The cervix was then dilated to 9mm during which a gas (Carbon Dioxide) hysteroscopy was performed to identify the cavity and to exclude false passages or perforation. MEA treatment then proceeded in standard fashion. [303] Patients were discharged with an information sheet and contact number once comfortable, voiding and tolerating diet.

4.2.3 Stastistical Analysis

180 patients were required to achieve 80% power to detect a 20% difference in satisfaction and a 10% difference in acceptability at the 5% significance level (Instat 2,Version 2). The baseline event rate for acceptability was derived from previous work on MEA by Wallage et al [300] that reported 85% of women finding MEA under local anaesthesia acceptable. This study was a randomised controlled trial of MEA under local anaesthesia versus general anaesthesia. In previous work from a randomised controlled trial of MEA versus Transcervical Resection of the Endometrium by Cooper et al [223] 77% of women in the MEA arm reported themselves totally or generally satisfied.
In total 210 women were recruited to account for a 15% drop out rate post treatment.
Analysis was by intention to treat. SPSS for Windows (Version 9 .0) was used to create the database and to perform statistical analysis. Independent and paired t tests were used to analyse continuous variables that were normally distributed. Mann- Whitney test was used for ordinal or continuous variables that were not normally distributed. Chi square or Fishers Exact Test for independent nominal data. 95% confidence intervals (CI) were calculated for normally distributed continuous variables and for differences in proportions for categorical data.

4.2.4 Economic Methods and Analysis

Health service costs consist of the costs prior to admission to hospital, during admission for the MEA procedure and throughout the recovery period (4 weeks). The cost of the hormone preparation treatment was estimated using the British National Formulary. [344] Anaesthetics, drugs and consumables were costed using local prices. Data from the Health Technology Board of Scotland were used to compute staffing costs[345] , Scottish Health Service data were used to cost the overheads. [346] Equivalent annual costs (based on replacement values) were computed to account for capital costs. [347] An average cost per procedure for the MEA equipment was obtained from a previous study.[348]

GP visits, clinic and hospital visits (including diagnostic tests, procedures and drugs) were cross checked using hospital records and valued using costs from the published literature. [312;349]

Data on non-health service costs were obtained using the two costing questionnaires Information was collected on the time and transport costs associated with obtaining the hormone preparation treatment and the hospital admission, companions accompanying patients on the day of the procedure, the cost of caring for dependents and other costs associated with the treatment. A standard cost per mile [312;350], and average wages for Scotland [312;351] were used to value transportation and time of patients, companions and dependent care givers. Values for other non-health service costs were directly obtained from the questionnaires. All costs data were presented in 2002 pound sterling (£) and exclude value added tax. The costing data was analysed using appropriate parametric and non-parametric tests. Bootstrapping, a statistical technique was used to compute limits around the estimates of total health and non-health service costs.

4.3 Results

Study recruitment was commenced in April 2001 and the last treatments completed on the 25th of July 2002.

210 women were randomised and 197 completed treatments- 97 were treated in the post menses arm and 100 treated in the standard drug preparation arm (See Fig. 1). The CONSORT scheme of study reporting was adhered to and Fig. 1 shows the flow of patients through the trial.

Patient baseline characteristics are recorded in Table 1. There was no significant difference in the number of patients with pathological anxiety or depression scores between the groups (p=0823 and p=0.783 respectively).[342]

4.3.1 Operative Details

The Research Fellow was trained to do MEA and performed 95% of the procedures; the Consultant in charge performed the remainder. Operating times and findings are presented in table 2.

One patient in the drug preparation arm had severe cervical stenosis and a false passage created, suspected and confirmed at hysteroscopy prior to MEA. She declined a further attempt at ablation at 6 weeks. Two patients in the drug preparation arm required general anaesthesia for pain (one during dilation, one during MEA treatment) no one in the post menses arm required rescheduling under general anaesthesia for procedure related pain or discomfort.

One patient required general anaesthesia in the post menses arm because of a significant vaso-vagal reaction. This responded rapidly to 0.6 mgms I.V. Atropine and occurred half way through the active MEA treatment itself. A Rollerball ablation under general anaesthetic was required at a later date to visualise and ablate the untreated part of the cavity.

One patient in each arm both who had had previous cone biopsies received cervical lacerations at dilation. The MEA procedures were performed completed and the lacerations sutured after the procedure under local anaesthesia.

4.3.2 Acceptability

In the six point Likert Scale categories of discomfort (none / mild / discomforting /distressing / horrible / excruciating) there were no significant differences between the groups (p= 0.614).

Greater levels of acceptability were recorded by women in the post menses group at two weeks post operation (See Table 2).
Two women in the post drug arm recorded that their procedure was either totally or generally unacceptable. All the women in the post menses arm recorded their procedure as acceptable.

Procedure discomfort was assessed by a modified McGill pain questionnaire. Patients were asked to compare the procedure to common experiences and rank them in order of severity; MEA ranked a higher score than an internal examination or cervical smear but was a lower score than worst head-ache, tooth-ache or stomach-ache. McGill Pain Scores by group (un-weighted) showed no significant difference between groups (p=0.944).

Intra-operative Midazolam usage was significantly higher in the post menstrual arm. There was a low and almost identical requirement for intra-operative opiate analgesia in both arms of the trial (Table 2).
Two women in the post drug arm required to be converted to general anaesthesia (GA) because of unacceptable levels of pain and anxiety. No one in the post menses arm required conversion.

The likely side effects of the endometrial preparation were assessed in both groups for the four weeks prior to their procedure. Comparing post menses group to the endometrial preparation group respectively the incidence of Hot Flushes was 23.9% vs. 69.7%, (p=0.001), Nausea 15.9% vs. 33.7% (p=0.006), Rashes/ Itch 4.5% vs. 15.7%(p=0.014) and Weight gain 15.9% vs. 39.3% (p=0.001).

After their procedure patients were asked how they would prefer to have a repeat operation. 91 (94.8%) in the post menses arm would arrange their treatment the same way again, in the post menses phase, telephoning for a date, and 5 (5.2%) would change to hormonal preparation.

In the drug prep arm 55 (56.1%) would arrange their operation the same way but 43 (43.9%) would prefer treatment after a period. In total if arranging their operation again 134 (69%, p= 0.001, 95%CI for difference in proportions 0.40, 0.61) opt for no preparation post menstrual MEA^{TM}.

By 3 days post operatively significantly more women in the post menses arm were back to normal activity 45 (46.4%) in the post menses arm and 28 (28%) in the post drug arm (p=0.008). The groups did not differ in the characteristics of their normal daily activities.

4.3.3 Satisfaction

Satisfaction was assessed on a six-point scale (totally satisfied / generally satisfied / fairly satisfied / fairly unsatisfied / generally unsatisfied / totally unsatisfied). There was no significant difference seen in satisfaction at 6 or twelve months. 90 (97.8%) in the post menses group and 91(93.8%) in the drug preparation group at 6 months reported themselves as totally or generally satisfied (p=0.746). At twelve months 86 (92.5%) in the post menses group and 84 (88.4%) in the drug preparation arm reported themselves as totally or generally satisfied (p=0.297).

4.3.4 Quality of Life

Quality of life scores (QOLS) were assessed. It is desirable to measure QOLS as they are demonstrably poorer in women with menorrhagia and have been shown to improve after ablative surgery.[15] Two different quality of life instruments are available to use; disease specific tool such as the Menstrual Distress Questionaire[352] or generic tools such as the SF 12 and SF36. The main benefit of disease specific instruments are that they pickup condition specific issues that may be missed in generic QOL tools . An example of this is the cyclical nature of menstrual problems which may reduce the validity of a generic tools result if the questionnaire was performed between symptoms. A benefit of the generic tools are that they allow a comparison between different and diverse disease groups and that certain tools (EUROQUOL) can be utilised in the calculation of economic related data such as quality adjusted life years(QUALYS). In this trial we utilised SF 12 (Version 1) Previous trials in Aberdeen have used SF 36. SF12 was chosen over SF 36 as it was shorter and less cumbersome. Unfortunately SF12 has not been validated in menorraghia, it has however been validated against SF36 which is valildated in menorraghia. The results for the Physical Component Summary and Mental Component Summary scores are shown in Fig 3. The improvements in QOLS for both categories from baseline to twelve months were significant ($p<0.001$) in both study groups but no significant difference was seen between groups. The values in both study groups were restored to normative values for an age matched healthy females. [341]

4.3.5 Menstrual Results

Menstrual data was available for 195 (99%) of the women at 6 months and 190 (96.4%) at 12 months. At 12 months 52 (55.9%) in the post menses arm and 60(61.9%) in the drug preparation arm were amenorrhoeic ($p= 0.405$). In those still menstruating 36 (87.8%) in the post menses arm and 33 (89.2%) in the drug preparation arm reported

their periods as no longer heavy. The median bleeding scores (for those still menstruating) and pain scores showed no statistically significant difference between the groups (Table 4). Regards further surgery there was one rollerball ablation in the post menses arm and one hysterectomy in the drug preparation arm by one year.

4.3.6 Economic Results

The main health services costs prior to admission are the prescription of the hormonal preparation. Overheads, staffing costs, capital costs (buildings and equipment), and consumables were the key items of resource during the hospital admission and throughout recovery. Resource use data collected by the clinical research fellow supplemented with information from the two-week clinical questionnaire.

The costing results are reported in Table 3. The mean cost for the total health service costs including endometrial preparation treatment, clinician visits to the ward, drugs, ward costs, costs of MEA procedure and GP visits post operative was £424 (95% CI £421 - £433) for the patients in the post menses arm of the study and £526 [95%CI £514 - £533) in the drug arm of the study. This difference between both arms of the study was statistically significant (p=0.001).

The mean cost for the total non-health service costs including patient travel costs, patient time costs during admission, companion travel costs, costs of caring for dependants, and other costs reported in the costing questionnaires was £146 (95%CI £119, £182) for patients in the post menses arm of the study and £135 (95%CI £113, £164) in the drug arm. (p=0.88).

4.4 Discussion

This study demonstrates that MEA™ performed under local anaesthetic, without endometrial preparation; in an outpatient setting is both acceptable and results in high levels of expressed satisfaction. MEA in the post menstrual phase results in comparable menstrual outcomes to standard treatment with endometrial preparation. It is a suitable technique for most women who wish to have an endometrial ablation as 69% of eligible patients referred for MEA™ are willing to consider treatment under local anaesthetic [353]whilst a normal cavity is not essential. It is reassuring that the effect on menstrual loss of not preparing the endometrium is not compromised. [301]

Generalisability of the results are enhanced by the avoidance of entry criteria based on menstrual bloods scores or predetermined uterine cavity regularity, a broad inclusion criteria with minimal exclusion criteria in this pragmatic trial. In addition a junior doctor taught microwave ablation just prior to the study commencing performed nearly all the procedures. The equipment utilised and local anaesthetic regimens adopted are available in the majority of health care facilities in the developed world. The results achieved in this study should therefore be genuinely reproducible and attainable.

Methodologically one could argue that the post randomisation dropouts compromise the results and that this does not represent a genuine intention to treat analysis in its purest sense. However there are different interpretations of intention to treat. As the dropouts did not receive treatment, no data collection was undertaken and the trial was not unbalanced it can be argued that intention to treat analysis has been achieved. The 8 post randomisation dropouts (5 in the post menstrual arm and 3 in endometrial preparation arm) were all contacted at the end of the trial to ascertain why they had not attended for treatment. They all reported that they no longer viewed their periods as a problem, had been reassured by their investigations and no longer desired treatment.

In a recent study 69% (223 out of 322) women referred for MEA would consider treatment under local anaesthesia. Women who expressed a preference for local anaesthesia did particularly well, with the majority commencing and being completed under local anaesthesia.[354] The majority entering this trial wished to avoid hormonal

endometrial preparation because of a desire to avoid the side effects of endometrial preparations.

The actual active microwave time was significantly shorter in the drug preparation arm reflecting the finding with first generation procedures of reduced operating times with thinner endometrium. Endometrial thickness as expected was significantly different. The post menses endometrium showed a considerable range compared to the predictable thin endometrium under hormonal manipulation. The thicker endometrium and more pronounced sub-endometrial vascular heat sink of an untreated cavity would theoretically dissipate some of the microwave energy leading to the prolonged treatment times seen. [301]. Whether this has an effect on long term clinical outcomes remains to be seen. Overall total operative times showed no significant difference between both groups.

The organisational issues of MEA in the post menstrual phase needs addressing. Whilst it was very easy for the dedicated research fellow to accommodate the 3 to 4 post menstrual patients on a Friday morning each week there are real logistical issues in providing a service that is dependant on patient's spontaneous onset of menstruation. This practical issue of coordinating unpredictable events such as the onset of menses and theatre lists or outpatient sessions is remedied by the use of timed withdrawal bleeds. The use of Provera 10 mgs B.D. for 10 days stopped ten days prior to treatment date allows the scheduling of treatments in the manipulated postmenstrual phase.

It is important to stress that the doses of sedative when used, were very small. There were no adverse events from the sedation doses even when combined with the use of intra –operative opiate analgesia with the vast majority of patients chatting through their procedure. The sedation was performed in strict accordance with the Royal Colleges Guidance document on the safe use of i.v. sedation. [355]

The difference in sedative use between the two arms of the trial is interesting. The patients were all counselled pre-operatively in the same fashion by the research fellow. It could be postulated that the knowledge that failure to tolerate the procedure in the post

menstrual outpatient arm would require rescheduling under general anaesthesia in 6 weeks time biased this arm towards accepting the offer of sedation more readily.
Significantly more women reported treatment post menses as totally or generally acceptable at two weeks (89%). A previous study randomising to MEA under general or local anaesthesia reported 97% vs. 85% respectively describing treatment as totally or generally acceptable. [356] Health service costs are statistically significantly lower for care provided in the outpatient setting. This modality could allow more patients to be treated with the same financial resources, shortening waiting lists and freeing up theatre space for other uses. The ability to move a traditionally theatre based treatment to an outpatient setting with its reduced costs is attractive, particularly in a private / commercial set up. The issue for the NHS is different. The financial irony is that the movement of any traditional theatre based procedure to a 'cheaper' low cost outpatient environment results in more work being done in different environments. Only if the vacated theatre or staffs are not otherwise utilised are financial savings made.

Many second-generation ablation techniques now exist with the aim of bringing safe, efficacious and simple to perform techniques to gynaecologist without specialist hysteroscopic surgical skills - Novasure device™ (bipolar ablation device) [225], ELITT ™ (multifibre diode-laser) [242],Thermachoice ™ [219] / Cavatherm [357] / Menotreat ™ (thermal balloon) [224], Hydro Thermablator ™ (hot water instillation techniques)[234], and Her-Option Device ™ (cryoablation). [358] Most require some type of endometrial preparation or have restrictions on cavity size /shape, or both. Some claim to be amenable to treatment using local anaesthesia but have not demonstrated this as a primary outcome measure in a randomised trial. Merely claiming the ability to undertake a procedure in a particular way does not demonstrate its acceptability, generalisability, effectiveness or efficiency. Good quality randomised control trials are needed to fulfil these requirements.
Long term clinical parameters will be followed up to compare satisfaction, menstrual outcomes and rates of further surgery in the two groups. Formal economic analysis over the long-term will compare the two methods in terms of further treatment required.

Menstrual outcome will be measured in the two groups up to one year. Clinical outcomes and subsequent surgery have significant effects on economics. The majority of repeat procedures and hysterectomies will take place within 18 months of surgery and rarely after 3 years, follow-up will cover that period.[182] The longer-term follow-up of these groups will reveal the true cost.

4.5 Conclusion

This trial demonstrates in the context of an adequately powered randomised controlled trial that Microwave endometrial ablation performed under local anaesthetic in the postmenstrual phase is an effective and efficient method of treating the majority of women who wish conservative surgical treatment for heavy menstrual loss. Treatment post menses avoids the side effects and significant costs of drug preparation. Treatment post menses is more desirable to women than treatment after endometrial preparation with the avoidance of preparation associated side effects being the main drive. The technique is rapid, achieving both high satisfaction and acceptability rates, whilst also achieving menstrual outcomes and rates of further surgery unmatched by other endometrial ablative techniques. There are demonstrable cost savings and also the potential benefit of releasing valuable operating theatre time and personnel for other operations which require these facilities.

These results encourage the development of outpatient MEA by providing good quality RCT based evidence of clinical efficacy and cost effectiveness. Outpatient treatment remains the logical development of endometrial ablation. The results of this trial establish the role of MEA in the outpatient setting and is timely given the recent approval of MEA (and Thermal Balloon Treatment) for the treatment of menorrhagia by NICE.[311]

Figure 1 – Study recruitment diagram

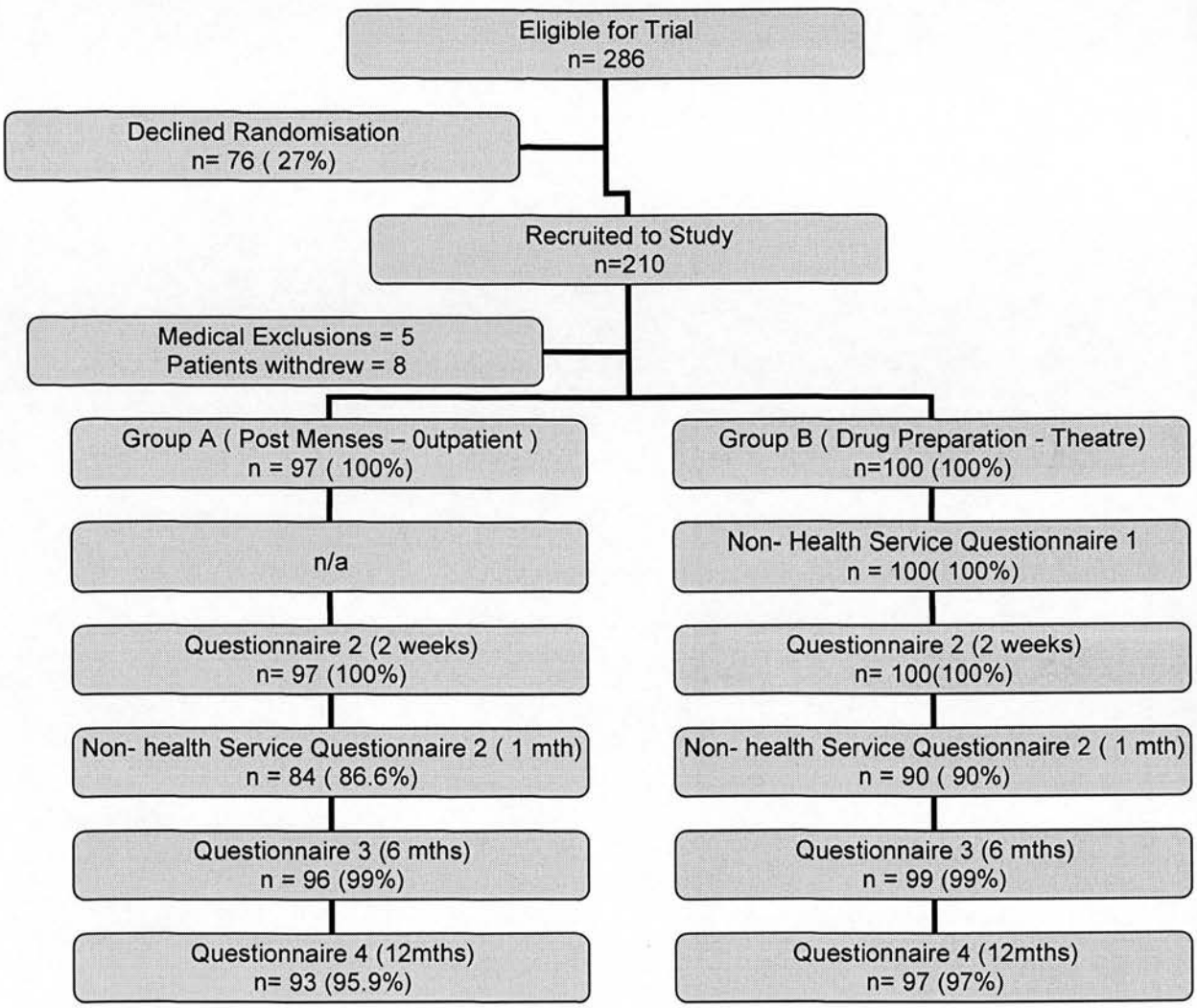

Table 1.

Values given are median (Inter Quartile Range { IQR}) or N (%)

Characteristics	Randomised to Post Menses Treatment (N=97)	Randomised to Drug Preparation (N=100)
Mean Age (SD)	42.36 (4.78)	42.41 (5.35)
No. of Vaginal deliveries	2 (0-5)	2 (0-4)
Women with no previous vaginal deliveries	17 (18.5)	11(11.0)
Previous caesareans	20 (20.6)	18(18)
Clots and or Flooding	92 (94.8)	98 (98)
Double protection	85 (87.6)	85 (88.5)
Premenstrual Dysmenorrhoea	62 (63.9)	59 (59.6)
Previous Cervical Surgery	13 (13.4)	9 (9.0)
Median Menstrual Pain Score* (IQR)	17 (10, 21.5)	14 (7, 21)
Median Bleeding Score* (IQR)	23 (19,29)	24 (19, 31)
Cavity Length / cm (range)	8.50 (5-11.5)	8.40 (6-13)
Regular cavity	81 (83.5)	86 (86.0)

* = Bleeding and pain scored from a minimum of zero to a maximum of 50.

Table 2 Acceptability / Post Operative

	Randomised to Post Menses Treatment (N=97)	**Randomised to Drug Preparation (N=100)**	**Significance at 5% level**
Totally/Generally Acceptable (Post op)	79 (84%)	72 (75.8%)	P = 0.157 CI 95% -0.03,0.20
Totally/Generally Acceptable (2 wks)	86 (89.5%)	76 (76%)	P = 0.012 CI 95% 0.03, 0.24
VisualAnalogue Scale TotallyAcceptable(0)-TotallyUnacceptable (10)	1.2	1.0	P= 0.735
Post Op Opiates	42 (42.4%)	22 (22%)	P= -0.001
Discharge at 6 hrs	79 (81.5%)	81 (81%)	P= 0.937
Overnight Stay	12 (12.4%)	20 (20%)	P= 0.147
Recommend to a friend	92 (95.8%)	86 (90.5%)	P= 0.145

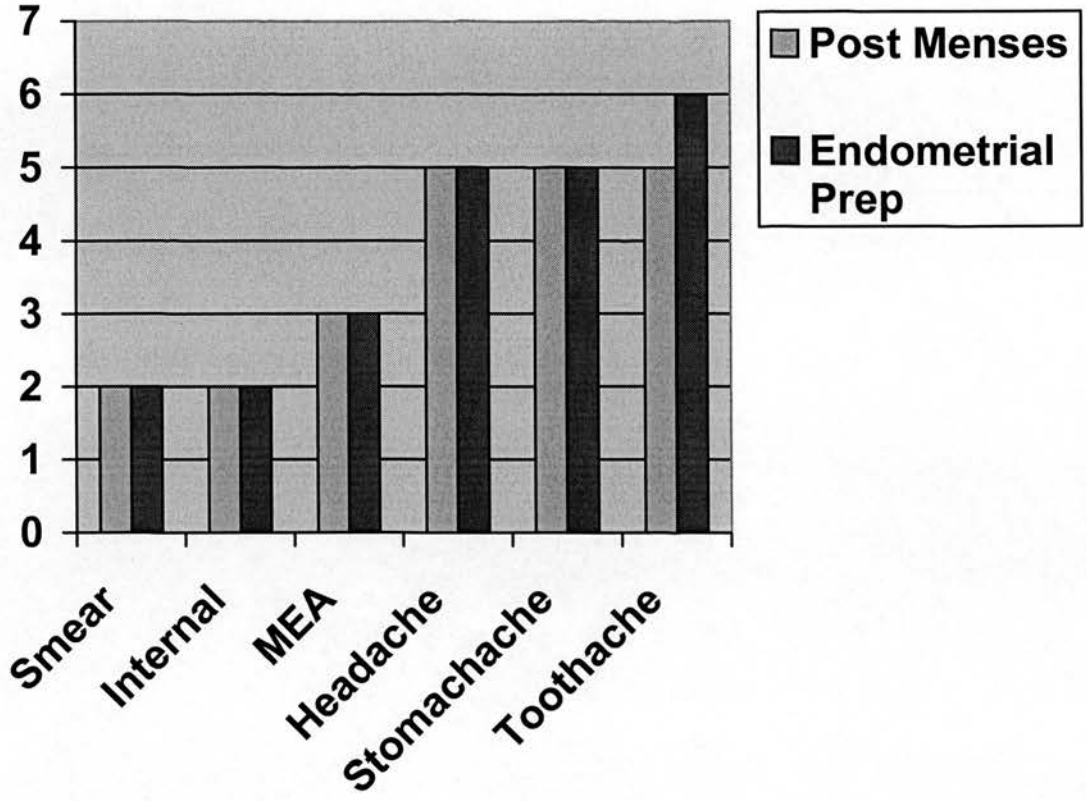

Fig 2 Procedure Related Discomfort (Modified McGill's – Median Scores)
(1= none, 2= mild, 3= discomforting, 4= distressing, 5= horrible, 6= excruciating)

Table 3 Procedure Data

	Randomised to Post Menses Treatment (N=97)	**Randomised to Drug Preparation (N=100)**	**Statistical significance**
Procedure Time / minutes	20 (12-35)	20 (12-35)	0.841 [a]
Microwave time / seconds	243 (105-475)	229 (132-458)	0.026 [a**]
Endometrial thickness (mm)	4 (1-14)	2 (1-11)	0.001 [a**]
Endometrial preparation			
None	94 (96.9)	0 (0)	
Danazol	2 (2.1)	85(85.0)	
Zoladex	1 (1.0)	9 (9.0)	
Both	0 (0.0)	6 (6.0)	

a = Mann Whitney Test

** = Significant at the 5% level.

Table 4 – Menstrual Outcome – values given as median (IQR) or N (%)

	Randomised to Post Menses Treatment (Max N=97)	**Randomised to Drug Preparation (Max N=100)**	**Statistical significance****
Totally / Generally Satisfied (12mths)	86 (92.5%)	84 (88.4%)	P= 0.341 CI -0.04, 0.13
Amenorrhoea (6 months)	50(52.1)	60 (60.6)	P=0.230 [b] CI -0.22, 0.05
Amenorrhoea (12 months)	52 (55.9)	60 (61.9)	P=0.405 [b] CI - 0.20, 0.08
Periods No Longer Heavy (12 months)	36 (87.8)	33 (89.2)	P=0.848 [b] CI -0.16, 0.13
Unchanged / Heavier period (12 months)	2 (4.9)	1 (2.7)	1.0 [c] CI -0.11, 0.06
Median Bleeding Score (IQR) (12 months)	5 (2, 8)	3 (2,5)	P=0.301 [a]
Median Pain Scores (IQR) (12 months)	4.5 (1.25, 7.75)	3 (2,6)	P=0.357 [a]

a = Mann Whitney Test

b = Differences in proportions $\chi 2$ test

c= Fishers Exact Test

** = Significant at the 5% level. All CI are 95%

Health service costs	Randomised to Post Menses Treatment				Randomised to Drug Preparation			
	Mean	**Median**	**Standard deviation**	**Minimum - Maximum**	**Mean**	**Median**	**Standard deviation**	**Minimum Maximum**
N	93				91			
Total cost at 12 months post surgery**	**£444**	**£417**	**£72**	**£396-£874**	**£568**	**£527**	**£245**	**£478-£2,803**
1 month post surgery								
Including								
N	97				100			
Endometrial preparation treatment	£2	£0	£13	£0-£122	£49	£34	£37	£34-£156
	£368	£364	£13	£356-£430	£413	£410	£11	£390-£448
MEA procedure -theatre & recovery								
Other drug costs	£6	£6	£2	£3-£9	£6	£6	£1	£3-£9
Ward costs	£36	£34	£15	£22-£75	£49	£44	£18	£27-£86
	£7	£0	£13	£0-£57	£11	£0	£17	£0-£77
GP visits								
Total	£426	£413	£32	£396-£620	£529	£512	£47	£478-£700
Further 11 months post surgery								
Including								
N	93				91			
GP visits	£11	£0	£31	£0-£153	£13	£0	£37	£0-£230
Clinic visits and hospital admissions	£7**P<0.001	£0	£49	£0-£362	£27	£0	£230	£0-£2,192
Total	£19	£0	£64	£0-£477	£40	£0	£244	£0-£2,307

***Table 4:* Health service costs at 12 months post surgery* Totals may not add up due to rounding.**

***P<0.001

Chapter 5

Endometrial Ablation versus Hysterectomy – a review of rates of surgery in the Grampian Region and Scotland 1998 – 2004.

5.1 Introduction

Hysterectomy remains a highly successful surgical procedure for the treatment of menorrhagia, guaranteeing amenorrhoea and achieving high satisfaction rates. Benign Hysterectomy rates vary both nationally and internationally, but are felt to be unacceptably high in the Western world. Countries like the United States[359] and Finland [287] have some of the highest reported rates of hysterectomy in the world (560 and 414 per 100,000 women respectively) in comparison other countries like Sweden and Norway have much lower rates (145 and 164 per 100,000 respectively).

It has been demonstrated that a number of factors may alter hysterectomy rates. Coulter et al reported that hysterectomy rates varied enormously (up to three fold difference) between different general practices.[314] . If referral per se is a risk factor for hysterectomy then factors that reduce referral may reduce hysterectomy. Work by Fender et al revealed that active education of 'good menorrhagia management' in primary care halved the numbers referred but doubled the risk of surgery in those referred [360]. Vessey [361] reported that lower social class , higher parity and older age were associated with increased likelihood of hysterectomy. However, the latter study was conducted amongst a selected population from the Oxford region that consisted of Caucasian, married women, aged 25-39 who were all willing to co-operate with follow up.
UK data from the early 1990's revealed that after 5 years of being referred to a gynaecologist with heavy menstrual bleeding, 60% of women have had a hysterectomy.[302] Furthermore, 20% of UK women have undergone a hysterectomy by the time they are 55 years old [314;362]. These figures precede the introduction and general

uptake of endometrial ablation and more recently the Levonorgestrel IUS. As 80% of women having hysterectomy had no demonstrable pathology the vast majority of hysterectomies could, it was predicted be replaced by ablations. A resulting reduction in hysterectomy was thus expected. Many felt the widespread use of ablation technology would result in a decrease in hysterectomies. Others remained to be convinced. They argued that hysterectomy rates would be unaffected in the long term. Arguments followed that the majority of endometrial ablations would require a hysterectomy in the future with patients merely temporising their ultimate definitive surgery.

Bridgman and Dunn [363] analysed hospital admissions data for women who underwent a hysterectomy or endometrial ablation for dysfunctional uterine bleeding in England and Wales between 1989 and 1996. They reported an initial rise in operation rates for endometrial ablation until 1992/3 following which the rates fell. They commented on the fact that hysterectomy rates have remained relatively steady since the introduction of endometrial ablation. They reported the total operation rates (hysterectomy and ablation combined) for dysfunctional uterine bleeding initially increased but then tended to fall after 1992/3. The ratios of hysterectomy to endometrial ablation for dysfunctional uterine bleeding troughing at 3:1 in 1992/3, but by 1995/6 had increased to 4:1. They concluded that rather than, as many had predicted, ablations replacing hysterectomy in the treatment of dysfunctional uterine bleeding, endometrial ablation appeared to have added an alternative operative technique. The knock on effect of this being an increase in the total number of operations for this condition and thus instead of reducing NHS expenditure it was actually increasing costs. They suggested a hypothesis that the less invasive nature of the ablative techniques would encourage women who would never consider a hysterectomy to seek a surgical procedure for their menorrhagia through a lowering of the threshold for intervention.

Reid et al have recently reviewed the trends in the numbers of hysterectomies and ablations in England for menorrhagia between 1989 and 2002-3. [364] NHS hospital episode statistics were analysed for the years 1989 -1990 and 2002 -2003. An average of

23,056 hysterectomies was performed per annum in England for menorrhagia in the period 1989 -1990 to 1994-1995. Since 1995-6 they demonstrated a progressive decline with 8332 hysterectomies performed in 2002-2003. Analysis of the number of ablations revealed that the shortfall in hysterectomies was not being made up in an increased number of ablations. The total number of operations for menorrhagia was seen to decrease. In total a 64% decrease in the number of hysterectomies and a 43% reduction in the total number of operations for menorrhagia were observed (23,284 vs. 13,252). Reid's data would suggest that the reduction in hysterectomy numbers is not explained by a concomitant increase in ablations. One potential explanation that has been proffered has been that the increasing use of the Levonorgestrel Intrauterine System (IUS) for treatment of menorrhagia has reduced the demand for hysterectomy. Licensed in 2001 for the treatment of menorrhagia the IUS has, it is assumed, been used extensively off license prior to this date. The device has been available as a contraceptive since 1995 coinciding with the decline in hysterectomies for menorrhagia. An ongoing RCT study to determine the 'Effectiveness and Cost-effectiveness of Levonorgestrel containing intrauterine system in Primary care against Standard treatment for menorrhagia' (ECLIPSE study) is being conducted by the NHS Health Technology Assessment Programme, which may determine whether indeed the IUS has had an effect on hysterectomy rates in England & Wales. The trial commenced in January 2004 with the aim of recruiting 1000 women aged 25-50 years presenting to their General Practitioners with menorrhagia, and not intending to become pregnant in the next 5 years. Subjects are randomly allocated to the Levonorgestrel-releasing intrauterine systems or standard medical treatment (combined oral contraceptive pill, tranexamic acid or mefenamic acid), based on the Royal College of Obstetricians and Gynaecologists (RCOG) guidelines. Outcome measures are effect on quality of life, patient satisfaction, hysterectomy rates and a cost effectiveness analysis. Follow up is intended for 6 months, 1, 2, 5 and 10 years.

Analysis of hysterectomy and endometrial ablation rates from Australia (New South Wales) from 1981 to 1994-1995 have been published.[365] The hysterectomy rate declined

by about 16% during 1981-1991 rising since; the endometrial ablation rate increased by 28% between 1991 and 1994-1995. They reported a trend towards older mean age at operation, a swing to vaginal hysterectomy with or without laparoscopy, a shift to private hospitals, and a dramatic decline in length of hospital stay. They concluded that the introduction of endometrial ablation techniques has had a major impact on hysterectomy rates.

The aim of the study reported in this chapter was to analyse the relationship of ablation to hysterectomy for menorrhagia in the Grampian Region (served by Aberdeen Royal Infirmary) and also the comparable Scottish national data.

5.2 Methods

With the assistance of the Information Management and Technology Department (IMT) of Aberdeen Royal Infirmary (Grampian figures) and NHS Scotland Information and Statistics Division (ISD) data (Scottish National Figures) on the numbers of endometrial ablations and benign hysterectomy were collected and analysed for women aged 20-55 years, both at Aberdeen Royal Infirmary and in Scotland between Jan 1998 and Dec 2004.

The ICD 10 (1996 onwards) codes were used. As there is no specific code for menorrhagia a number of different codes were used. The codes for endometrial ablation were -Microwave Endometrial Ablation – Q17.4 + Y11.4, Trans Cervical Resection of the Endometrium – Q 17.1, Thermal Balloon Ablation – Q 17.4 + Y11.8, Hysteroscopic Endometrial Ablation - Q 17.4 + Y08.8.

For Hysterectomy the codes used were Total Abdominal Hysterectomy – Q07.(all) , Vaginal Hysterectomy – Q 08.2, Laparoscopically Assisted Vaginal Hysterectomy (any route)– Q 08.2 + Y50.8 plus diagnostic codes – N92 (= menstrual) / D 25.9 (= fibroid) .Hysterectomies for pain, prolapse or malignancy were excluded.

5.3 Results

5.3.1 National Data

The Scottish National Data was collected with the assistance of the ISD department of NHS Scotland using SMOR1 data. The data is represented in Table 1.

Table 1 Scottish Benign Hysterectomy and Ablation 1998- 2004.

Operation / Year	1998	1999	2000	2001	2002	2003	2004
Benign Hysterectomy	6609	5788	5026	4694	4277	3964	3792
1st Generation Ablation	812	858	930	932	936	941	720
2nd Generation Ablation	507	755	978	933	955	1171	1461
Total Number of Procedures	7928	7401	6934	6559	6168	6076	5973
Ratio (Hysterectomy : Ablations)	5:1	3.6:1	2.6:1	2.5:1	2.3:1	1.8:1	1.7:1

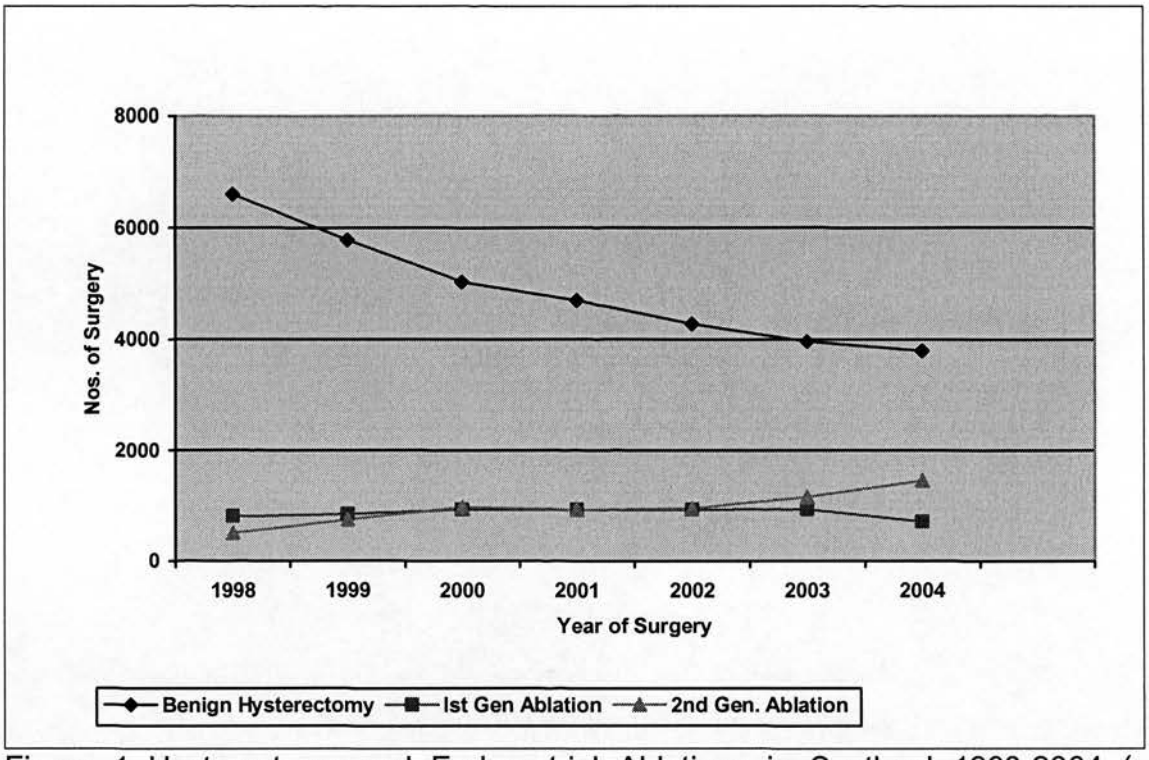

Figure 1 Hysterectomy and Endometrial Ablations in Scotland 1998-2004 (women aged 25-55years)

The number of ablations (first and second generation) performed in Scotland increased by 65 % over the time frame from 1319 per annum in 1998 to 2181 in 2004. A drop of 11% in the number of first generation ablations and an increase of 65% in the number of second generation ablations was reported. The total number of surgical procedures for menorrhagia (ablation plus hysterectomy) fell from 7928 in 1998 to 5973 in 2004 (25% reduction). (Table 8.1). The ratio of hysterectomy to ablation fell from 5: 1 in 1998 in 1998 to 1.7: 1 in 2004.

Sub analysis of the operative route for hysterectomy was performed. The number of abdominal hysterectomies for menorrhagia fell from 5637 in 1998 to 3264 in 2004 (a drop of 42%). The number of vaginal hysterectomies for menorrhagia fell from 799 in 1998 to 545 in 2004 (a fall of 31%) also the number of Laparoscopically Assisted

Vaginal Hysterectomy (LAVH) for menorrhagia fell from 173 in 1998 to 74 in 2004 , (a drop of 57%) over the seven year period.

Table 2 Grampian Benign Hysterectomy and Ablation 1998 -2004

Operation/ Year	1998	1999	2000	2001	2002	2003	2004
Benign Hysterectomies	205	146	146	137	165	122	136
Endometrial Ablation	221	277	335	285	256	305	347
Total Number of Procedures	426	423	481	422	421	427	483
Ratio Hysterectomies to Ablations	0.9: 1	0.5:1	0.4:1	0.5:1	0.6:1	0.4:1	0.4:1

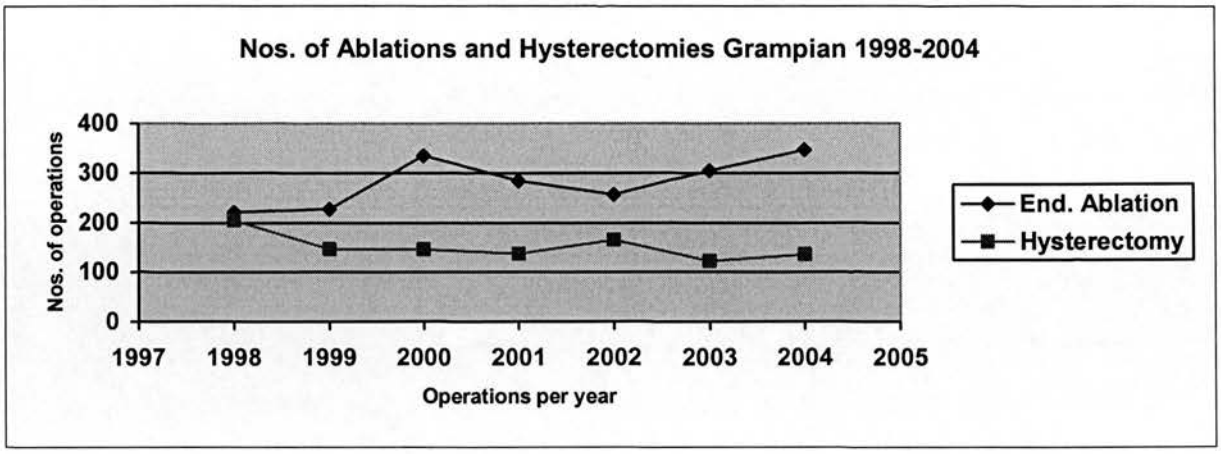

Figure 2 Numbers of Endometrial Ablations and Hysterectomies in Grampian 1998-2004.

Between 1998 and 2004 in Grampian Region a 34% reduction in hysterectomy rates was observed. Endometrial ablation increased by 57% in the same time period. Comparing the figures for the total number of procedures there was a 13% increase in the total number of procedures performed. Looking at the ratio of ablation to hysterectomy reveals a move from a ratio of almost equivalence with 0.9:1 ratio of ablations to hysterectomy to a ratio in 2004 of 0.4: 1.

5.4 Discussion

Looking at the National data first there has been a smaller drop in the number of hysterectomies performed in Scotland than reported in the Reid paper for England.[364] A 43% drop in the number of hysterectomies performed in Scotland between 1998 and 2004 can be compared to the 64% decrease reported by Reid & Mukri for period 1989-2003. The time scales are different but the overall trend is the same. Looking at the hysterectomy data for the more comparable period 1998 -2003 in Reid's paper shows a fall from 15 hysterectomies per 1000 to 8 per 1000, a 46% drop which is very similar to the 43% drop in the Scottish data. An overall reduction of 25 % in procedures performed

for menorrhagia is noted less than the 43% reduction reported by Reid et al. [364] The ratio of Hysterectomy to Ablation in Scotland fell from 5: 1 in 1998 to 1.7:1 in 2004.

Looking at the decrease in the numbers of hysterectomy by route is revealing. Why the drop in LAVH is more marked when compared to abdominal and vaginal hysterectomy is difficult to say but may relate to a wearing off of the 'honeymoon effect' associated with any new technology or treatment modality. The higher complication rate reported in the Evaluate trial may also be an important factor.[277;324;325] The drop in vaginal hysterectomies is on balance more concerning. The vaginal route when compared to the abdominal route has much in its favour including more rapid recovery, reduced post operative ileus, reduced postoperative complications, reduced analgesia use, reduced inpatient days and faster return to normal activity.[325] Many feel that more hysterectomies should be performed vaginally. The question of whether more women would be suitable for vaginal hysterectomy was asked by the group from the Endoscopy Training Centre at the Royal Free Hospital who analysed a group of 500 women who underwent hysterectomy to assess their suitability for vaginal surgery.[366] In this population 96 (19.2%) women underwent vaginal hysterectomy whereas the group estimated that 382 (76.4%) women could have had the procedure vaginally. Lack of uterine prolapse (76.4%), uterine fibroids (44.5%), and a need for oopherectomy (43.2%) were the three most common reasons for choosing the abdominal route. The group suggested an increased familiarity in the surgical techniques for dealing with non-prolapsed uteri, uterine fibroids, and vaginal oopherectomy would increase the vaginal hysterectomy rate. Training issues may be in part to blame. Shortened career paths, reduced operative exposure and opportunities may impact on the favored routes of vaginal surgery. A UK National Survey of experience and attitudes to vaginal hysterectomy revealed that that senior trainees' (SpR 4 and 5) experience in vaginal as opposed to abdominal hysterectomy was relatively poor. However, despite this, trainees believed that the majority of hysterectomies should be done vaginally, and only a minority, abdominally.[367]

Looking at the ablation data for Scotland the 65 % increase over the time frame is notable and goes against Reid's observation of a fall in the number of ablations performed. A drop of 11% in the number of first generation ablations and an increase of 65% in the number of second generation ablations was reported in Scotland. The total number of surgical procedures for menorrhagia (ablation plus hysterectomy) fell from 7928 in 1998 to 5973 in 2004. (Table 8.1). The ratio of hysterectomy to ablation fell from 5 : 1 in 1998 (similar to Bridgeman and Dunn's figures[363]) to 1.7: 1 in 2004 .

A 25% reduction in the total number of procedures performed in Scotland in the1998 – 2004 time frame is reported, this is less than the 43 % reduction seen in England between 1989 and 2003. The Grampian region population is predominantly Caucasian, static and served by one major teaching hospital, thus making it perhaps unrepresentative of the larger Scottish population.

The numbers of hysterectomies in Grampian dropped by 34% over the time scale 1998 - 2004. This is less than that reported by Reid et al [364] in England in an equivalent time scale and that recorded in the Scottish data. The Grampian Ablation data is slightly at odds with that seen in Scottish data, a 57% increase in Ablations is reported in comparison with to the 65% increase in Scotland. This may represent the fact that the Grampian Consultants had already adopted ablation techniques in 1998 and thus proportionally, the increase in the number of ablations in 2004 is less evident than in the rest of Scotland. Grampian region has a very pro-ablation consultant body with a number of internationally recognised ablationists practicing at Aberdeen Royal Infirmary. If the Scottish figure for reduction in surgery for menorrhagia is less than for England & Wales (25% versus 43%) then the reduction in Grampian is even less marked with a reduction of 13% noted. The ratio of Hysterectomy to Ablation in Grampian is also strikingly different with a ratio of 5:1 reducing to a ratio of 1.7:1 seen in the Scottish data over the time period 1998 to 2004 compared to a ratio of 0.9 :1(almost equality) reducing to 0.5:1 in the Grampian data. This data is at odds with the English ratios produced by Bridgeman and Dunn which reported a 3:1 ratio of hysterectomy to

ablation in 1992/3 increasing to a 4:1 ratio in 1995/6. Looking at the Grampian data the smaller reduction in rates of surgery for menorrhagia and the greater rates of ablation compared to hysterectomy may represent the strong preference to ablations in Aberdeen. It is also notable that the number of ablations in Grampian has remained relatively static whilst the hysterectomy figures have continued to decrease. This might suggest that perhaps the use of Mirena has had an effect on the number of operations for menorrhagia. It is difficult to estimate the effect of the Levonorgestrel IUS Mirena on the Grampian and Scottish surgical figures. The launch of IUS as a contraceptive in 1995 coincides with the start of the drop off in English hysterectomy and a cause and effect is postulated.[364] A significant amount of off license use is assumed to have taken place before it was finally licensed for menorrhagia in 2001, but unfortunately, we have no hard data to back this hypothesis up. The ECLIPSE trial should help unravel the epidemiological issues around the role Levonorgestrel IUS has in menorrhagia.

5.5 Conclusion

Rates of surgery do not remain static but show dynamic changes over time. A variety of influences on the rates of surgery exist and some are easier to assess than others. Hysterectomy will always remain an effective and definitive procedure that offers cure of menorrhagia but at a price. The optimal route of hysterectomy is vaginal and it is concerning that the preferred route of surgery is still abdominal in Scotland (3264 versus 545). The role of endometrial ablation is established and long-term data is encouraging that the rates of further surgery remain low. A shift from the more operator dependant technically difficult 1st generation ablative techniques to the second generation ablative techniques is seen in the Scottish figures. How much the procedure of ablation replaces hysterectomy is more difficult to say. Hysterectomy rates have fallen as ablation rates increase but whether this is pure cause and effect and how much of an impact is brought with the Levonorgestrel IUS is more difficult to untie, hopefully further studies in the pipeline will reveal this.

The lowering of the threshold for surgery suggested by Bridgeman and Dunn is interesting and such an effect may be expected in a pro-ablation region like Grampian. Ablation in Grampian is almost now twice as common (2004 data) as hysterectomy and contrast markedly to the national ratios for hysterectomy to ablation which fell from 5 : 1 in 1998 in 1998 to 1.7: 1 in 2004. Which ratio is optimal is difficult to say. The small (13%) reduction in operative procedures in Grampian may represent a lower overall impact on total operative procedures caused by patients who would never consider hysterectomy opting for ablation. Whether this is an undesirable effect is debatable. This potential switching of patients who would never consider hysterectomy and therefore be managed medically to ablation would increase operative rates and theatre usage. However, as observed in the study of long-term follow up after ablation reported in chapter 2 of this thesis, patients that were randomised to surgical (ablation) had superior outcomes in terms of higher satisfaction scores and quality of life when compared to those randomised to medical treatment. Thus, perhaps better patient outcomes in the long-term may be realised with greater uptake of endometrial ablation with improved patient outcome and avoidance of the cost to the NHS and patients of long-term medical treatment.

Chapter 6

Conclusions arising from the work presented in this thesis and suggested areas for future research.

This thesis has centred on excessive menstrual bleeding and in particular the role and evidence base of endometrial ablative surgery.

In chapter one the aetiology, epidemiology and treatment options were reviewed. As a condition excessive menstruation exerts a significant health care burden with an estimated cost to the country of 7 million pounds per annum in medical treatments and a similar amount on surgery.[100]
Rates of surgery vary significantly both nationally and internationally with data from the 1990's reporting 60% of women referred to a gynaecologist being hysterectomised within 5 years.[314] Ablations rates also vary with conflicting views on the long-term effect of ablations on hysterectomy rates.
Medical treatments can be effective and to some are the only acceptable treatment but most RCT evidence is poor. The trial evidence suffers from small numbers, with short term follow up and a cross over design with patients acting as their own control group.

In chapter two I reported on a five year follow up of a RCT offering women referred with menorrhagia either current best practice medical therapy or ablative surgery. This represents the longest follow up of patients treated medically. The numbers persisting with medical treatment long term was minimal, with 77% in the medical arm undergoing surgery (18% a hysterectomy). Interestingly the hysterectomy rate in the ablated arm was almost identical (17%) to that in the medical arm. The QOL scores in the ablation arm were superior to those in the medically treated arm with all eight scales of the SF36 health survey scores restored to normative values and only 4 being restored in those treated medically despite the majority receiving ablation over the trial interval. This trial

establishes the hierarchy of treatment (with the comment that the trial predates the use of the Mirena Levonorgestrel IUS). Medical treatment in this trial resulted in poorer QOL outcomes, patient satisfaction with smaller numbers who would recommend it to a friend. This trial establishes medical treatment as inferior to ablative surgical treatment which in turn is inferior to hysterectomy. The trial also addressed the potential effects of early ablation, a policy many are concerned will have a negative impact on overall rates of surgery. The policy of offering early ablative surgery in those referred to a gynaecologist with excessive menstrual bleeding did not increase the hysterectomy rate in this trial and more over was associated with improved outcomes. These results are highly generalisable into the wider clinical population with the limited inclusion criteria and pragmatic study design.

In chapter three I report on a RCT of MEA versus RBEA. Worldwide RBEA is a common ablative procedure. In North American especially RBEA is the commonest first generation ablative procedure. The trial establishes MEA to be as effective as RBEA in the measured outcome variables.
The trial design has certain features. The unbalance randomisation ratio (2:1, MEA: RBEA) was designed to maximise the numbers in the experimental treatment arm. Some negative exist. The strict inclusion criteria and objectification of menorrhagia decrease generalisability of the trial and may result in exaggerated outcomes compared to those seen in a general clinical population. The influence of a competing commercial interest must also be borne in mind as a potential for bias. Overall the trial can be seen to give RCT evidence that MEA gives comparable outcomes to RBEA.

In chapter four MEA outpatient ablation in the post menstrual phase was assessed. Many would argue that outpatient therapy is the natural progression of the second generation ablative procedures. The simplicity of technique and short operative times lend these procedures to use in this setting. Transferring out of a high cost labour intensive theatre environment into a low cost environment has many advantages. Many ablative technologies claim acceptability as outpatient techniques. Looking at the quality of the

data however reveals little evidence of this being assessed as a primary outcome measure in adequately powered RCT. The evidence base for the majority of technologies claim of suitability for outpatient treatment is derived from small non randomised and inherently biased case series.

The reported trial reveals the economic benefits of outpatient ablative surgery with a significant financial saving, a mean of £ 124 less than standard treatment. The treatment was also highly acceptable to the trial participants with significantly more women finding post menses outpatient treatment acceptable compared to treatment in an operating theatre as a day case (89.5% versus 76.0%). The numbers in each arm reporting themselves as totally or generally satisfied with their treatment were similar. Importantly menstrual outcomes were unaffected by the avoidance of endometrial preparation with similar menstrual outcomes in each arm. This is reassuring as there was concern about the possibility of reduced efficacy in the absence of endometrial preparation. Thus this trial established outpatient MEA in the postmenstrual phase as a feasible proposition, that endometrial preparation was not essential and that post menstrual treatment was not only acceptable but indeed more acceptable than standard drug preparation.

Overall the feasibility of post menstrual outpatient treatment remains unfortunately slightly questionable. Whilst it is undoubtedly possible in the context of a RCT with a dedicated research fellow and well motivated support staff certain aspects may make it more difficult to introduce into routine care. The logistics of scheduling patients into treatment slots on the basis of their menses is a problem in its self. Also for those who are intolerant of the procedure there is the question of rescheduling under general anaesthesia. These practical issues are in conflict with the desirability of the procedure as an outpatient. At present treatments in Aberdeen Royal Infirmary are scheduled after an artificially induced withdrawal bleed (Provera 10mgs is taken twice daily for 10 days and stopped 10 days prior to surgery). This result in the patient being in the early postmenstrual phase at the time of surgery. This allows patients to be scheduled into standard operating lists. A second issue is post operative pain and nausea. Unfortunately whilst a well tried pre / intra-operative regime of analgesia plus or minus conscious

sedation exist there remains the issue of post operative pain. Post operative pain is unpredictable and may necessitate admission. Certainly in Aberdeen with many patients living over 30 miles away this is a real problem which would prevent the use of ablation as an outpatient therapy off site. Analgesia use post operatively was high with 43.3%(post menses) and 22% (post endometrial preparation) requiring opiates and similar numbers around 81% being fit for discharge at 6 hours the majority of the remainder requiring overnight stay.
Overall the trial establishes MEA as feasible, economically advantageous and successful as a post menstrual outpatient treatment.

In chapter five rates of ablative surgery and hysterectomy were assessed. An over view of the Scottish and Grampian data was made with comparison to comparable English data. The 1990's figure of 60% hysterectomy rates at 5 year are now compared to the more recent figures after the general uptake of ablation of 18%. The pro – ablation stance of Aberdeen may well infact result in a reduction in hysterectomy but at a cost of an increase in the total number of procedures (ablation + hysterectomy). In Scotland the ratio of ablation to hysterectomy is in the order of approximately 2 to 1 whilst the Grampian data suggest almost the opposite ratio of 2 ablations for every hysterectomy.

Certain trends in the national figures give cause for concern with the numbers of vaginal hysterectomies remaining disproportionably small. Training issues may have a role to play in this. The drop in laparoscopically assisted vaginal hysterectomies is also a concern, training issues again may again be in part responsible for this.

6.1 Suggestions for Future Research

Major inroads into the management of menorrahagia have been achieved; however significant deficiencies in our knowledge still exist. New and promising treatment modalities require further evaluation. Adequately powered, randomsied controlled trials with adequate periods of follow up would make a significant and effective contribution to the medical knowledge base.A pragmatic design utilising both economic outcomes

and health related quality of life as a outcome would be highly desirable. Quality of life tools should ideally include both generic and disease specific tools.

6.1.1 Genetics

Further work is required into the genetic basis of endometrial dysfunction. Human genomics and proteonomics may well hold the key to unlock the label of dysfunctional uterine bleeding. The basis of the disease is likely to lie in abnormal gene expression. Borthwick et al have established the transcript profile for human endometrium in normal endometrium of the secretory and proliferative phases of the menstrual cycle.[368] Work reported form Cambridge in the late nineties established the feasibility of in vivo gene transfer in murine endometrium and in vitro gene transfer in human endometrial preparations.[165] This work using DNA - lipososme complexes described by Charnock – Jones et al [165] is highly significant and may be the first step along a road away from steroid agonists and antagonists and towards a directed gene therapy.

6.1.2 Medical Treatments

The epidemiology of Mirena use in menorrhagia needs to be addressed. The long term outcome of Mirena users needs to be defined. The exact numbers persisting with the device over a 10 -15 year interval is unknown.

Mirena has been compared to hysterectomy and limited ablation data is available but has been hard to come by. Now that evidence is accruing of the feasibility and acceptability of outpatient ablation the comparison with IUS is even more valid. The recruitment difficulties experienced by the previous RCT of Mirena verus ablation need to be overcome either through different study design or larger multicentre trials.

Further research into the mechanism and treatment of irregular bleeding seen with the IUS is required. These side effects are commonly sited as a reason for discontinuation and premature removal. Endometrial Hyperplasia (with or without atypia) as a pathological group are often treated with Mirena especially in patients who are

unattractive for surgery (e.g. severe medical problems / morbid obesity). There is little evidence however as to the safety of this treatment versus standard oral progestagen regimes and this represents an area for research.

The management of fibroids remains surgically dominated. The longterm outcome of Uterine Artery Fibroid Embolisation require further evaluation especialliy as many studies only involved a 6 – 12 mth follow-up period.How many women will still retain their uterus at 5 years remains to be established. The role of repeat embolisation also remains to be clarified.
The suitability of Mirena in irregular or large cavities (e.g. fibroid cavities) is unknown , studies into the use in such cavities would aid in patient counselling and management.

New oral medical treatments exist that may offer a treatment option for fibroid associated menorraghia. These may offer potentially a longterm (unlike GnRHa) fertility sparing medical option.
Progesterone receptor anatagonists have been used. Mifepristone has proved useful in the management of unwanted pregnancy and miscarriage and in the induction of labour. A systematic review of 3 studies of the use of Mifepristone in the medical treatment of fibroids revealed promising menstrual symptom relief, reduction of fibroid volume and pressure symptoms but a rather worrying level of hyperplastic change.[369]
Asoprisinil is a SPRM (Selective Progesterone Receptor Modulator) that shows some early promise in the medical treatment of both menorraghia and fibroids. Dose dependant suppression of menstrual blood loss, reduction in fibroid volume and pressure effects have been demonstrated with preservation of ovulation and the basal oestrogen levels remaining unchanged. No adverse effect on the endomeruim was reported. Further research is highly desirable.[370;371]

6.1.3 Education

The taboos and misconceptions surrounding menstruation are unhelpful. The development of educational programmes to educate and empower women may, over the long term reduce hospital referrals. Qualitative research into exactly why women seek referral performed without the constraints and censorship implicit in a questionnaire would prove illuminating.

6.1.4 Endometrial Ablation

The acceptability of ablation under local anaesthesia needs to be assessed in adequately powered randomised control trials for each method that claims to be suitable as an outpatient treatment. Long term safety and outcome data of all second generation ablative treatments are required, a 'MISTLTOE 2 'study is long overdue. Safety issues must remain at the forefront of our minds. Whilst the newer techniques may not lend themselves so easily to a Mistletoe style audit this should not deter us from being vigilant. The usefulness of device specific data collection by national bodies such as the US FDA MAUDE Database is to be bourn in mind.
Long term concerns regarding the effect on the incidence, presentation and prognosis of endometrial cancer need to be addressed through epidemiological studies.
Further head to head RCT of different ablation modalities require to be performed especially in the context of outpatient treatment. The role of ambulatory or ' one stop' menstrual clinics (including the uses of see and treat ablation clinics) requires to be defined. Their usefulness, safety, cost effectiveness and acceptability to patients require evaluation.

6.1.5 Diagnostic Tests

The role and ideal combination of diagnostic tests in the investigation of menstrual disturbance requires evaluation. Th exact combination of history taking, clinical

examination, endometrial evaluation and medical imaging that would provide efficient , cost effective and acceptable (from a patients perspective) investigation requires to be defined. [372] Further investigation into the role bleeding disorders have to play in the presentation and management of menstrual disorders is desirable. Von Willibrands disease is common but no easy test exists that could be applied effectively to the population with menstrual problems. Further scientific developments into rapid, effective and cheap tests of coagulation are desirable.

6.2 Conclusion

The work highlighted in this thesis represents my clinical interest in menstrual disorders and their treatment. I wish to thank the women who agreed to take part in the research that this thesis is based upon and the assistance and support of Drs Cooper and Cameron. The evolution through medical and surgical treatments and their development represents a body of work that has taken a number of years to complete and longer to evolve into a literary piece. A family has been started and completed in the same time frame.
My interest continues to evolve as the treatment of menstrual disorders improves immeasurably from the days when all roads led to hysterectomy.

Appendix 1. Study Questionnaires

1.1Chapter 5 TCRE versus Medical: Five year follow-up questionnaire.

Study No ..... Original treatment Medical / T.C.R.E.

The study you took part in about five years ago for treatment of heavy periods is now finishing and the questionnaire enclosed is the final part of the project. You were allocated the above treatment originally, although we realise that you may have had other treatments since then. We would be grateful if you could take some time to complete the questionnaire as best you can and return it in the pre-paid envelope. If you feel that you are still having problems with your periods and would like to be seen again then please say so at the end.

Thank you for your help and time

1/ Have your periods	stopped	☐ 1
	continued but lighter	☐ 2
	continued as before	☐ 3
*** if stopped, then go straight to question 8***	continued but heavier	☐ 4
2/ How many days are there from the first day of one period to the first day of the next ?	less than 21	☐ 1
	21 to 35	☐ 2
	more than 35	☐ 3
	totally unpredictable	☐ 4
3/ On average, for how many days does your	less than 3 days	☐ 1

period last ?

between 3 and 7 days ☐ 2
between 8 and 10 days ☐ 3
more than 10 days ☐ 4

4/ On average, for how many days is the bleeding heavy ? ☐ 1

5/ Do you have pain with your period ?

no ☐ 1
less than before ☐ 2
same as before ☐ 3
worse than before ☐ 4

6/What is an average period like for you now ? For each day please show how severe your
bleeding and pain are by giving each day a score from 1 to 5
(1 is mild bleeding/pain, increasing up to 5, the worst bleeding/pain you can think of)

Day of Period	Bleeding score	Pain score
1	☐	☐
2	☐	☐
3	☐	☐
4	☐	☐
5	☐	☐
6	☐	☐
7	☐	☐
8	☐	☐
9	☐	☐
10	☐	☐

7/ Do your periods stop you from carrying out your work, housework or other daily activities ?

- no, not at all ☐ 1
- no, but work suffers ☐ 2
- yes, but only one day ☐ 3
- yes, more than one day ☐ 4

8/ What further treatment have you had for your periods since the original treatment that you were given in the study?

- tablets (name below) ☐ 1
- T.C.R.E. ☐ 2
- repeat / second T.C.R.E. ☐ 3
- hysterectomy ☐ 4
- other (explain below) ☐ 5

9/ Do you get any of the following symptoms just before or during a period, or on a cyclical basis if you are not having periods?

	Yes	No
breast discomfort	☐ 1	☐ 2
bloatedness	☐ 1	☐ 2
irritability	☐ 1	☐ 2
headaches	☐ 1	☐ 2
depression	☐ 1	☐ 2

10/ Is sexual intercourse painful for you ?

- no ☐ 1
- yes, but less than before ☐ 2
- yes, the same as before ☐ 3
- yes, worse than before ☐ 4

11/Since your treatment are you experiencing any new or different pelvic pain ?

- no ☐ 1
- sometimes ☐ 2
- regularly ☐ 3

12/ Overall, what effect has your treatment so far had on your period symptoms ?

No effect	1
improved, but not sufficiently	2
improved to an acceptable level	3
cured completely	4

13/ Have you found your treatment acceptable ?

Yes	1
No	2

14/ What treatment would you recommend to a friend with heavy periods?

Medical (tablets)	1
T.C.R.E. operation	2
Hysterectomy	3
None	4

15/ Please indicate how you would rate your overall satisfaction with your treatment.

(please circle the number that is closest for you)

1	2	3	4	5	6
totally satisfied	generally satisfied	fairly satisfied	fairly dissatisfied	generally dissatisfied	totally dissatisfied

The following questions ask for your views regarding your health and how you feel about life in general. Answer all the questions, if you are unsure then think about your overall health and give the best answer you can.

1/ In general, would you say your health is ? (circle one)

excellent..... 1

very good..... 2

good..... 3

fair 4

poor 5

2/ Compared to a year ago, how would you rate your general health now ? (circle one)

much better..... 1

somewhat better..... 2

about the same 3

somewhat worse 4

much worse 5

3/ The following questions are about activities you might do during a typical day. Does your health limit you in these activities ? If so, how much ?(circle one number for each question)

ACTIVITIES	YES, LIMITED A LOT	YES, LIMITED A LITTLE	NO, NOT LIMITED AT ALL
a/ vigorous activities, such as running, lifting heavy objects or strenuous sports ?	1	2	3
b/ moderate activities such as moving a table, hoovering ,bowling or golf ?	1	2	3
c/ lifting or carrying groceries ?	1	2	3
d/ climbing several flights of stairs ?	1	2	3
e/ climbing one flight of stairs ?	1	2	3
f/ bending, kneeling or stooping ?	1	2	3
g/ walking more than a mile ?	1	2	3
h/ walking half a mile ?	1	2	3
I/ walking 100 yards	1	2	3
j/ bathing or dressing yourself	1	2	3

4/ During the past 4 weeks , have you had any of the following problems with your work or other regular daily activities as a result of your physical health ?

(circle one number for each question)

	YES	NO
a/ cut down on the amount of time you spent on work or other activities ?	1	2
b/ accomplished less than you would have liked ?	1	2
c/ were limited in the kind of work or activities ?	1	2
d/ had difficulty performing the work or other activities (e.g it took extra effort)?	1	2

5/ During the past 4 weeks , have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	YES	NO
a/ cut down on the amount of time you spent on work or other activities ?	1	2
b/ accomplished less than you would have liked ?	1	2
c/ didn't do work or other activities as carefully as usual ?	1	2

6/ During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with friends, family or groups ?

(circle one)

not at all 1

slightly .....

2

moderately 3

quite a bit 4

extremely 5

7/ How much bodily pain have you had in the past 4 weeks ?

(circle one)

none	.....	1
very mild	.....	2
mild	.....	3
moderate	.....	4
severe	.....	5
very severe	.....	6

8/ During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework) ?

(circle one)

not at all	.....	1
a little bit	.....	2
moderately	.....	3
quite a bit	.....	4
extremely	.....	5

9/ These questions are about how you feel and how things have been with you during the past 4 weeks.

For each question, please give the one answer that comes closest to the way you have been feeling. (circle one number for each question)

HOW MUCH TIME IN THE LAST 4 WEEKS	ALL OF THE TIME	MOST OF THE TIME	A GOOD BIT OF THE TIME	SOME OF THE TIME	A LITTLE OF THE TIME	NONE OF THE TIME
a/ did you feel full of life ?	1	2	3	4	5	6
b/ have you been nervous ?	1	2	3	4	5	6
c/ have you felt so down in the dumps that nothing could cheer you up ?	1	2	3	4	5	6
d/ have you felt calm and peaceful ?	1	2	3	4	5	6
e/ did you have a lot of energy ?	1	2	3	4	5	6
f/ have you felt downhearted and low ?	1	2	3	4	5	6
g/ did you feel worn	1	2	3	4	5	6

out ?						
h/ have you been happy ?	1	2	3	4	5	6
I/ did you feel tired ?	1	2	3	4	5	6
j/ Has your health limited your social activities?	1	2	3	4	5	6

10/ How TRUE or FALSE is <u>each</u> of the following statements for you (circle one number for each question)

	DEFINITELY TRUE	MOSTLY TRUE	DON'T KNOW	MOSTLY FALSE	DEFINITELY FALSE
a/ I seem to get ill more easily than other people	1	2	3	4	5
b/ I am as healthy as anybody I know	1	2	3	4	5
c/ I expect my health to get worse	1	2	3	4	5
d/ My health is excellent	1	2	3	4	5

1.2 Chapter 6 MEA versus REA Trial Questionnaire

A COMPARISON BETWEEN ROLLERBALL ENDOMETRIAL ABLATION AND MICROWAVE ENDOMETRIAL ABLATION

Rollerball endometrium ablation (REA) versus microwave endometrial ablation (MEA.)

We would like to invite you to participate in a study comparing two methods of treating the lining of your womb (endometrial ablation) as treatment for heavy periods. The study is part of a research project to promote medical knowledge in this area of gynaecology, but may be of no benefit to you personally.

The following information should give you more of an understanding of what the study is trying to find out, but if you have any further questions then please ask. Please be aware that there is absolutely no obligation to participate in the study. Even if you did decide to take part, you can change your mind and withdraw from the study at any time, for any reason, without explanation, and your care will not be affected.

Each month a lining (endometrium) forms inside the womb and is shed as your period. Sometimes this bleeding can become heavy and even unpredictable. Removing this lining can result in periods stopping altogether or becoming lighter. It has been decided that this is the most appropriate treatment for your heavy periods. There are many different ways of destroying the endometrium. Passing an instrument up through the neck of the womb (cervix) usually when you are asleep performs them all. The commonest method world-wide at present is to perform a rollerball ablation, which involves destroying the lining using a small electric ball.

Another newer way of destroying the womb lining to a predictable depth is to use a microwave probe. Both techniques are proven to be safe, successful and acceptable treatments and are performed in exactly the same way. Indeed you would not know

which technique you had received unless you were told. Both REA and MEA are used in Aberdeen and have been for some time.

REA and MEA have never been compared with each other to determine whether there are any advantages of one technique over the other .

To find out how useful treatments are doctors need to do a study. If you were to take part in this study comparing MEA and REA you would be allocated to having one or other operation by chance. You would have a two out of three chance (66%) of having a MEA and a one in three chance (33%) of a REA. We would ask you to complete questionnaires before the operation and at two weeks, three, six, twelve and twenty-four months afterwards. These would allow us to find out how effective each technique is at treating heavy periods, but particularly how acceptable each operation is and whether MEA is quicker and easier to perform.

In addition we would want to take a blood sample to measure two female hormones, FSH and oestradiol (5 teaspoonfuls / 10 mls of blood). These blood tests are taken at the beginning and repeated six months and one year after your operation to tell us whether you are close to the menopause

It is important to add that neither operation guarantees that you cannot fall pregnant in the future, although it is unlikely. If you wish, a sterilisation can be performed at the same time as the operation, which should not increase your stay in hospital.

Dr Stuart Jack
Clinical Research Fellow

PROTOCOL: Randomized Controlled Trial to Assess the Effectiveness of Microwave Endometrial Ablation (MEA) Versus Rollerball Endometrial Ablation (REA) for the Treatment of Menorrhagia PAGE: 1	MICROSULIS	PATIENT INITIALS: ☐☐ PATIENT NO: ☐☐☐

RECRUITMENT QUESTIONNAIRE

This questionnaire is completely confidential. When completing, please **read the instructions carefully, take your time and be honest.** If you cannot answer a particular question, leave it out and we will go through it with you later.

NAME	
ADDRESS	
TELEPHONE	
AGE IN YEARS	
DATE OF BIRTH	
NAME OF YOUR DOCTOR	
DOCTOR'S ADDRESS	
DOCTOR'S PHONE NO.	

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Pt. Initials & Date

PROTOCOL: Randomized Controlled Trial to Assess the Effectiveness of Microwave Endometrial Ablation (MEA) Versus Rollerball Endometrial Ablation (REA) for the Treatment of Menorrhagia

PAGE: 2

MICROSULIS

RECRUITMENT QUESTIONNAIRE (continued)

PATIENT INITIALS: ☐☐☐

PATIENT NO: ☐☐☐☐

Please specify answer by checking the appropriate box to the right.

1.	How long have you suffered from heavy periods?	Less than one year	
		One to three years	
		More than 3 years	
2.	Would you describe your periods as	Light	
		Moderate	
		Heavy	
		Very heavy	
3.	On average, for how many days does your period last?	Less than 3 days	
		Between 3 and 7 days	
		Between 8 and 10 days	
		More than 10 days	
4.	On average, for how many days is the bleeding heavy?	Not heavy	
		1 to 3 days	
		4 to 6 days	
		7 or more days	

5. Imagine an average period for you; for each day please show how severe your bleeding and pain were by giving each day a score from 0 to 3 (0=none, 1=mild, 2=moderate, 3=severe)

Day of Period	Bleeding	Pain
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		

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Pt. Initials & Date

PROTOCOL: Randomized Controlled Trial to Assess the Effectiveness of Microwave Endometrial Ablation (MEA) Versus Rollerball Endometrial Ablation (REA) for the Treatment of Menorrhagia PAGE: 3	MICROSULIS **RECRUITMENT QUESTIONNAIRE (continued)**	PATIENT INITIALS: ☐☐☐ PATIENT NO: ☐☐☐☐

Please specify answer by checking the appropriate box to the right.

6.	Do your periods stop you from carrying out your work outside the home?	No, not at all	
		No, but work suffers	
		Yes, but only one day	
		Yes, more than one day	
7.	Do your periods interfere with household and/or leisure activities?	No, not at all	
		Mildly affected	
		Moderately affected	
		Severely affected	
		Totally prevents it	
8.	At any time in the last three months, have you needed to use more than one form of protection at the same time?	No	
		Tampon and pads	
		Tampon and two pads	
		More than this (e.g. towel)	
9.	On your heaviest day, how many tampons and/or pads do you use?	Number of tampons	
		Number of pads	
10.	Do your periods occur at regular intervals (ie. The same time every month)?	Yes	
		No	
11.	On average, how many days are there between the start of one period and the start of the next period?	_____days	

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Pt. Initials & Date

PROTOCOL: Randomized Controlled Trial to Assess the Effectiveness of Microwave Endometrial Ablation (MEA) Versus Rollerball Endometrial Ablation (REA) for the Treatment of Menorrhagia PAGE: 4	MICROSULIS **PREOPERATIVE INCLUSION CRITERIA**	PATIENT INITIALS: ☐☐☐ PATIENT NO: ☐☐☐☐ DATE: ☐☐☐☐☐☐

	INCLUSION CRITERIA (All questions must be answered YES) Please specify by checking the appropriate box to the right.	**Yes**	**No**
1.	**SELECT ONE COLUMN TO THE RIGHT & CHECK THE APPROPRIATE CATEGORY BELOW** Previous Documentation of menorrhagia – 1month PBLAC Previous diagnosis failed medical therapy_____ Pt. refused medical therapy (document on source doc.)_____ Pt. was unable to tolerate medical therapy (document on source doc.)_____ PBLAC score _____ >/= 185 (RECORD SCORE)		
2.	No previous documentation of menorrhagia – 3month PBLAC PBLAC scores _____, _____, _____(average) >/= 185 (RECORD SCORES)		
3.	FSH measurement _____ mI. U/ml < 30		
4.	Negative pregnancy test		
5.	Negative endometrial sampling		
6.	Uterine cavity length _____ cm < 14		
7.	Age>/= 30 years		
8.	Patient agrees not to use hormonal contraception or other interventions for abnormal uterine bleeding for the duration of the study		
	SPECIAL PRECAUTIONS		
1.	Long term steroid use		
2.	Connective tissue disorder		
3.	Bicornuate uteri		
4.	Acutely retroverted or fixed uterus		

Signature: _____ **Date:** _____

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PROTOCOL: Randomized Controlled Trial to Assess the Effectiveness of Microwave Endometrial Ablation (MEA) Versus Rollerball Endometrial Ablation (REA) for the Treatment of Menorrhagia

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MICROSULIS

PREOPERATIVE EXCLUSION CRITERIA

PATIENT INITIALS: ☐☐☐

PATIENT NO: ☐☐☐☐

DATE: ☐☐☐☐☐☐

EXCLUSION CRITERIA (All questions must be answered NO) Please specify by checking the appropriate box to the right.		**Yes**	**No**
1.	**SELECT ONE COLUMN TO THE RIGHT AND COMPLETE INFO BELOW IF APPLICABLE** Does the patient have submucosal fibroids, polyps, or fibroids that obstruct treatment access to any part of the uterine cavity (as determined by hysteroscopy or U/S)? Fibroids _____ Size _____ Number _____ Type _____ Polyps _____ Obstructing Cavity _____ Location _____		
2.	Previous endometrial ablative surgery?		
3.	Previous classical cesarean section		
4.	Presence of IUD?		
5.	Patient who is pregnant or still desires to conceive?		
6.	Presence of atypical endometrial hyperplasia (i.e. adenomatous) or Endometrial carcinoma on preoperative endometrial sampling?		
7.	Presence of active endometritis?		
8.	History of gynecological malignancy within past five years?		
9.	Active Pelvic Inflammatory Disease (PID)?		
10.	Known clotting defects or bleeding disorders?		
11.	Untreated/unevaluated cervical dysplasia?		
12.	Thickness of uterine wall < 8mm		
13.	Uterus sounds < 6cm		

Signature: _____ **Date:** _____

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PROTOCOL: Randomized Controlled Trial to Assess the Effectiveness of Microwave Endometrial Ablation (MEA) Versus Rollerball Endometrial Ablation (REA) for the Treatment of Menorrhagia

PAGE: 6

MICROSULIS

PHYSICAL EXAM

PATIENT INITIALS: ☐☐☐

PATIENT NO: ☐☐☐☐

1. Date of Birth: ☐☐ (Mo.) ☐☐ (Day) ☐☐ (Yr.)

2. Race: (check one)
- ☐ 1=Caucasian
- ☐ 2=Black
- ☐ 3=Oriental
- ☐ 4=Hispanic
- ☐ 5=Other (Specify _____ __)

MEDICAL HISTORY

CODE: 1=Normal (Condition or Function) 2=Abnormal

STATUS: 1=Resolved 2=Existing

	Body System	Code	Specify Abnormality	Status
1.	Skin	☐	_____	☐
2.	Eyes, Ears, Nose & Throat	☐	_____	☐
3.	Respiratory	☐	_____	☐
4.	Cardiovascular	☐	_____	☐
5.	Musculoskeletal	☐	_____	☐
6.	Gastrointestinal	☐	_____	☐
7.	Genito-Urinary	☐	_____	☐
8.	Endocrine & Metabolic	☐	_____	☐
9.	Neurological	☐	_____	☐
10.	Psychological	☐	_____	☐
11.	Hematopoietic/Lymphatic	☐	_____	☐
12.	Allergies	☐	_____	☐
13.	Other (Specify) _____	☐	_____	☐

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SURGICAL HISTORY

Does the patient have a history of prior surgical procedures? (1=Yes*; 2=No) ☐

*if Yes, Complete the following listing:

DATE	Surgical Procedure(s):
Mo. Day Yr.	
Mo. Day Yr.	
Mo. Day Yr.	
Mo. Day Yr.	
Mo. Day Yr.	
Mo. Day Yr.	
Mo. Day Yr.	
Mo. Day Yr.	
Mo. Day Yr.	
Mo. Day Yr.	
Mo. Day Yr.	

PROTOCOL: Randomized Controlled Trial to Assess the Effectiveness of Microwave Endometrial Ablation (MEA) Versus Rollerball Endometrial Ablation (REA) for the Treatment of Menorrhagia

MICROSULIS

PHYSICAL EXAM

PATIENT INITIALS: ☐☐☐

PATIENT NO: ☐☐☐☐

VITAL SIGNS, HEIGHT AND WEIGHT

Oral Temperature: ☐☐☐ (°F) Respiration Rate: ☐☐ / minute

Pulse Rate: ☐☐☐ / minute Blood Pressure: ☐☐☐ / ☐☐☐ mmHg

Weight: ☐☐☐ (lbs.) Height: ☐☐ (inches)

PHYSICAL EXAMINATION

CODE: 1=Normal
2=Abnormal
3=Not Done

		CODE	Specify Abnormality
1.	Head, Neck & Thyroid	☐	
2.	Ears, Nose & Throat	☐	
3.	Eyes	☐	
4.	Chest (including breasts)	☐	
5.	Lungs	☐	
6.	Heart	☐	
7.	Lymph Nodes	☐	
8.	Abdomen	☐	
9.	Anorectal	☐	
10.	Genitalia	☐	
11.	Skin	☐	
12.	Musculoskeletal	☐	
13.	Neurological	☐	
14.	Other _____	☐	

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Signature: _____ Date: _____

PROTOCOL: Randomized Controlled Trial to Assess the Effectiveness of Microwave Endometrial Ablation (MEA) Versus Rollerball Endometrial Ablation (REA) for the Treatment of Menorrhagia

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MICROSULIS

PREOPERATIVE EXAM

PATIENT INITIALS: ☐☐☐

PATIENT NO: ☐☐☐☐

DATE: ☐☐☐☐☐☐

PHYSICAL EXAM: INDICATE IN RIGHT COLUMN	PREVIOUS DOCUMENTATION	PERFORMED
Pap smear (if not within last 6 mo.)		
Endometrial biopsy (if not within last 6 mo.)		
Uterine sounding _____cm		
U/S		
Uterine wall thickness _____mm		
Hysteroscopy		

Is the uterine cavity within normal limits?	YES	
	NO	
Are fibroids present?	YES	
	NO	

If fibroids are present, describe EACH with regard to size, type, location:

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PROTOCOL: Randomized Controlled Trial to Assess the Effectiveness of Microwave Endometrial Ablation (MEA) Versus Rollerball Endometrial Ablation (REA) for the Treatment of Menorrhagia

MICROSULIS

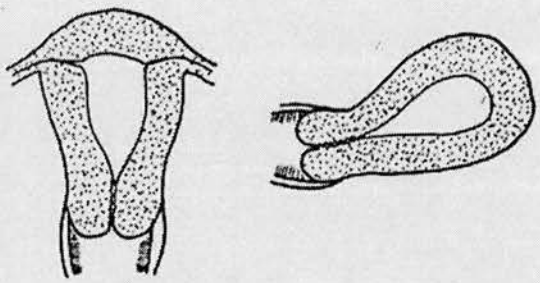
PREOPERATIVE EXAM (continued)

PATIENT INITIALS: ☐☐☐

PATIENT NO: ☐☐☐☐

DATE: ☐☐☐☐☐☐

USE DIAGRAM TO INDICATE POSITION AND SIZE OF FIBROIDS AND/OR POLYPS:



Are polyps present?	YES	
	NO	
Is treatment access to the uterine cavity obstructed?	YES	
	NO	

OTHER FINDINGS:

SIGNATURE: _____ DATE: _____

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PROTOCOL: Randomized Controlled Trial to Assess the Effectiveness of Microwave Endometrial Ablation (MEA) Versus Rollerball Endometrial Ablation (REA) for the Treatment of Menorrhagia PAGE: 11	MICROSULIS **Operative Form**	PATIENT INITIALS: ☐☐☐ PATIENT NO: ☐☐☐ DATE: ☐☐☐☐☐☐

	Fill in the blanks and/or mark the appropriate box to the right.		
1.	What procedure was performed?	MEA	
		REA	
		Resection/REA	
		Hysterectomy	
2.	Were there any intraoperative complications?	Failed instrumentation	
	Please use page 12-B to DESCRIBE complications and detail WHY they occurred.	Uterine perforation	
		Inadequate view	
		Hemorrhage	
		Equipment failure	
		Bowel damage	
		Urinary tract damage	
		Fluid overload	
		Major vessel damage	
		Uterine catheter required	
		Other _____	
3.	If uterine perforation occurred was it with...	Sound	
		Dilator	
		Hysteroscope	
		MEA applicator	
		Resectoscope	
4.	Was the procedure abandoned?	Yes	
		No	
5.	Special precautions.....	None	
		Connective tissue disorder	
		Long term steroid therapy	
		Bicornuate uteri	
		Acute retroverted uterus	
6.	How long was the operative time?	_____Seconds (MEA)	
		_____Minutes (REA)	
7.	What was the total anesthesia time?	_____Minutes	

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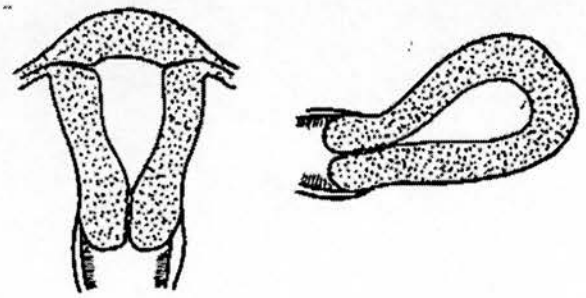
PROTOCOL: Randomized Controlled Trial to Assess the Effectiveness of Microwave Endometrial Ablation (MEA) Versus Rollerball Endometrial Ablation (REA) for the Treatment of Menorrhagia PAGE: 12	MICROSULIS **Operative Form (continued)**	PATIENT INITIALS: ☐☐☐ PATIENT NO: ☐☐☐☐ DATE: ☐☐☐☐☐☐

Fill in the blanks and/or mark the appropriate box to the right.

8.	Recovery room time (observation)	_____ Minutes	
9.	If laparoscopy was performed, was this.....	Planned	
		Diagnostic	
		Emergency	
		Sterilization	
		LUNA	
10.	Hysteroscopy		
A.	Is the uterine cavity within normal limits? Cavity length _____	Yes	
		No	
B.	Are fibroids present?	Yes	
		No	
C.	If fibroids are present, describe each with regard to size, type, location:		

USE DIAGRAM TO INDICATE POSITION AND SIZE OF FIBROIDS AND/OR POLYPS:



Signature: _____ Date: _____

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PROTOCOL: Randomized Controlled Trial to Assess the Effectiveness of Microwave Endometrial Ablation (MEA) Versus Rollerball Endometrial Ablation (REA) for the Treatment of Menorrhagia PAGE: 12 A	MICROSULIS **Operative Form (continued)**	PATIENT INITIALS: ☐☐☐ PATIENT NO: ☐☐☐☐ DATE: ☐☐☐☐☐☐

Fill in the blanks and/or mark the appropriate box to the right.

10.	Hysteroscopy (continued)		
D.	Are polyps present?	Yes No	
E.	Is treatment access to the uterine cavity obstructed?	Yes No	
F.	Other findings:		
11.	Was post op pain relief required in recovery?	Yes No	
12.	Was readmission required? (If YES, document)	Yes No	
13.	What type of anesthesia was used?	General Anesthesia IV Sedation Regional	
14.	For REA, fluid deficit post procedure	_____ mls	
15.	What was the operative stay of the patient?	_____ hours _____ days _____ nights	

Signature: _____ **Date:** _____

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PROTOCOL: Randomized Controlled Trial to Assess the Effectiveness of Microwave Endometrial Ablation (MEA) Versus Rollerball Endometrial Ablation (REA) for the Treatment of Menorrhagia PAGE: 12 B	MICROSULIS **Operative Form (continued)**	PATIENT INITIALS: ☐☐☐ PATIENT NO: ☐☐☐☐ DATE: ☐☐☐☐☐☐

PLEASE USE THIS FORM TO DETAIL ANY INTRAOPERATIVE COMPLICATION. INCLUDE WHAT COMPLICATION OCCURRED AND WHY.

Signature: _____ **Date:** _____

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PROTOCOL: Randomized Controlled Trial to Assess the Effectiveness of Microwave Endometrial Ablation (MEA) Versus Rollerball Endometrial Ablation (REA) for the Treatment of Menorrhagia

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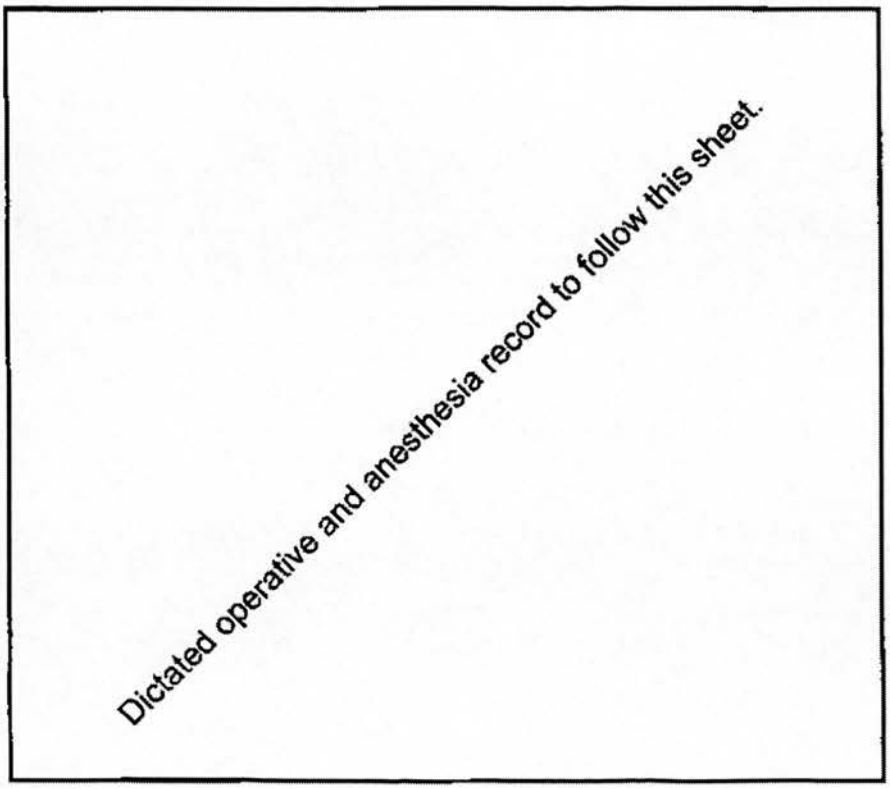
MICROSULIS

Detailed Dictated Operative Note

PATIENT INITIALS: ☐☐☐

PATIENT NO: ☐☐☐☐

DATE: ☐☐☐☐☐☐



SIGNATURE OF INVESTIGATOR: _____ DATE: _____

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PROTOCOL: Randomized Controlled Trial to Assess the Effectiveness of Microwave Endometrial Ablation (MEA) Versus Rollerball Endometrial Ablation (REA) for the Treatment of Menorrhagia PAGE: 14	MICROSULIS **NEXT DAY ASSESSMENT QUESTIONNAIRE**	PATIENT INITIALS: ☐☐ PATIENT NO: ☐☐☐ DATE: ☐☐☐☐☐☐

	Please check the appropriate box to the right.	YES	NO
1.	Have you experienced any nausea or vomiting?		
2.	Have you experienced a fever >101?		
3.	Have you experienced chills?		
4.	Have you experienced difficulty or pain with urination?		
5.	Have you experienced difficulty or pain with BM?		
6.	Are you experiencing excessive abdominal bloating?		
7.	Have you experienced uterine cramping unrelieved by pain medication?		
8.	Have you experienced any vaginal bleeding greater than 1 pad/hour?		

DOCUMENT ANY SYMPTOMS ANSWERED "YES" ABOVE. (If needed use AE comment form)

SUBJECTIVE COMMENTS:

ASSESSMENT:

PLAN:

RTO (2 WEEKS FROM PROCEDURE +/- 2 DAYS):

COORDINATOR'S SIGNATURE _____ **DATE:** _____

INVESTIGATOR'S SIGNATURE _____ **DATE:** _____

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PROTOCOL: Randomized Controlled Trial to Assess the Effectiveness of Microwave Endometrial Ablation (MEA) Versus Rollerball Endometrial Ablation (REA) for the Treatment of Menorrhagia

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MICROSULIS

Two-Week Post Operative Questionnaire

PATIENT INITIALS: ☐☐☐

PATIENT NO: ☐☐☐☐

	Please answer by checking only one box to the right.		
1.	How long after the procedure did you feel that you had completely recovered?	I have not recovered yet	
		Less than 2 weeks	
		2 to 4 weeks	
2.	When were you able to return to your normal everyday activities (housework, work, etc.)	Less than 2 weeks	
		2 to 4 weeks	
3.	Since the operation are you experiencing any new or different pelvic pain?	No	
		Sometimes	
		Regularly	
		Continually	
4.	Did you find the operation acceptable?	Yes	
		No	
5.	Did you require additional pain relief after going home?	Yes	
		No	
6.	If so, for how many days?	Next day	
		1-2 days	
		3-4 days	
		1 week	
		1-2 weeks	
		I have not stopped yet.	

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Pt. Initials & Date

PROTOCOL: Randomized Controlled Trial to Assess the Effectiveness of Microwave Endometrial Ablation (MEA) Versus Rollerball Endometrial Ablation (REA) for the Treatment of Menorrhagia PAGE: 16	MICROSULIS **Two Week Post Operative Questionnaire (continued)**	PATIENT INITIALS: ☐☐☐ PATIENT NO: ☐☐☐

7.	Is so, what kind?	Aspirin	
		Acetaminophen	
		Ibuprofen	
		Other, please specify	
8.	How often are/were you taking pain mediation?	One time/day	
		Two times/day	
		Three times/day	
		Four times/day	
		Five times/day	
		Six times/day	
		More than six times/day	
9.	How much medication are/were you taking at each dosing? (Please specify dose amount, i.e. 200 mg)	One tablet	
		Two tablets	
		Three tablets	
		More than three tablets	
10.	Have you experienced a "watery discharge" resulting from the healing from your treatment?	Yes	
		No	

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Pt. Initials & Date

PROTOCOL: Randomized Controlled Trial to Assess the Effectiveness of Microwave Endometrial Ablation (MEA) Versus Rollerball Endometrial Ablation (REA) for the Treatment of Menorrhagia PAGE: 16 a	MICROSULIS **Two Week Post-op Form**	PATIENT INITIALS: ☐☐☐ PATIENT NO: ☐☐☐☐ DATE: ☐☐☐☐☐☐

	Please answer by checking only one box to the right.		
1.	What date was the procedure performed?	/ / MONTH DAY YEAR	
2.	What procedure was performed?	MEA	
		REA	
		REA/RESECTION	
		HYSTERECTOMY	
3.	Has the patient used any medications since the procedure? (If YES, record on Concomitant Medication CRF)	YES	
		NO	
4.	Has the patient experienced any adverse events since the procedure? (If YES, record on the Adverse Events CRF)	YES	
		NO	
5.	Were there any post-op complications? (If YES, document below)	YES	
		NO	
6.	Was the pelvic exam at today's visit within normal limits? (If NO, detail below And record on the Adverse Events CRF)	YES	
		NO	
7.	Detail action taken if the 2 week pelvic exam was not within normal limits:		
	SIGNATURE OF INVESTIGATOR:_____	DATE:_____	

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PROTOCOL: Randomized, Controlled Trial to Assess the Effectiveness of Microwave Endometrial Ablation (MEA) Versus Rollerball Endometrial Ablation (REA) for the Treatment of Menorrhagia

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MICROSULIS

PATIENT INITIALS: ☐☐☐

PATIENT NO: ☐☐☐

Three Month Follow-up Questionnaire

	Please answer by checking only ONE box to the right.		
1.	How long after the procedure did you feel that you had completely recovered?	I have not recovered yet	
		Less than 2 weeks	
		2 to 4 weeks	
		4 to 8 weeks	
		2 to 3 months	
2.	When were you able to return to your normal everyday activities (housework, work, etc.)	Less than 2 weeks	
		2 to 4 weeks	
		4 to 8 weeks	
		2 to 3 months	
		Still unable	
3.	Have your periods	Stopped	
		Continued but lighter	
		Continued as before	
		Continued but heavier	
4.	Do you have pain with your period?	No	
		Less than before	
		Same as before	
		Worse than before	
5.	Do your periods stop you from carrying out your work outside the home?	No, not at all	
		No, but work suffers	
		Yes, but only one day	
		Yes, more than one day	

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Pt. Initials & Date

PROTOCOL: Randomized Controlled Trial to Assess the Effectiveness of Microwave Endometrial Ablation (MEA) Versus Rollerball Endometrial Ablation (REA) for the Treatment of Menorrhagia PAGE: 18	MICROSULIS **Three Month Follow-up Questionnaire (continued)**	PATIENT INITIALS: ☐☐☐ PATIENT NO: ☐☐☐☐

6.	Do your periods interfere with household and/or leisure activities?	No, not at all	
		Mildly affected	
		Moderately affected	
		Severely affected	
		Totally prevents it	
7.	Since the procedure are you experiencing any new or different pelvic pain?	No	
		Sometimes	
		Regularly	
		Continually	
8.	Did you find the operation acceptable?	Yes	
		No	
9.	Please indicate how you would rate your overall satisfaction with your treatment	Very satisfied	
		Satisfied	
		Dissatisfied	

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Pt Initials & Date

PROTOCOL: Randomized Controlled Trial to Assess the Effectiveness of Microwave Endometrial Ablation (MEA) Versus Rollerball Endometrial Ablation (REA) for the Treatment of Menorrhagia

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MICROSULIS

PATIENT INITIALS: ☐☐☐

PATIENT NO: ☐☐☐☐

Six Month Follow-up Questionnaire

	Please answer by checking only ONE box to the right.		
1.	How long after the procedure did you feel that you had completely recovered?	I have not recovered yet	
		Less than 2 weeks	
		2 to 4 weeks	
		4 to 8 weeks	
		2 to 3 months	
		3 to 6 months	
2.	When were you able to return to your normal everyday activities (housework, work, etc.)	Less than 2 weeks	
		2 to 4 weeks	
		4 to 8 weeks	
		2 to 3 months	
		3 to 6 months	
3.	Have your periods	Stopped	
		Continued but lighter	
		Continued as before	
		Continued but heavier	
4.	Do you have pain with your period?	No	
		Less than before	
		Same as before	
		Worse than before	
5.	Do your periods stop you from carrying out your work outside the home?	No, not at all	
		No, but work suffers	
		Yes, but only one day	
		Yes, more than one day	

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Pt. Initials & Date

MICROSULIS

Six Month Follow-up Questionnaire (continued)

PATIENT INITIALS: ☐☐☐

PATIENT NO: ☐☐☐☐

6.	Do your periods interfere with household and/or leisure activities?	No, not at all	
		Mildly affected	
		Moderately affected	
		Severely affected	
		Totally prevents it	
7.	Since the procedure are you experiencing any new or different pelvic pain?	No	
		Sometimes	
		Regularly	
		Continually	
8.	Did you find the operation acceptable?	Yes	
		No	
9.	Please indicate how you would rate your overall satisfaction with your treat-	Very satisfied	
		Satisfied	
		Dissatisfied	

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Pt. Initials & Date

PROTOCOL: Randomized Controlled Trial to Assess the Effectiveness of Microwave Endometrial Ablation (MEA) Versus Rollerball Endometrial Ablation (REA) for the Treatment of Menorrhagia

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MICROSULIS

PATIENT INITIALS: ☐☐

PATIENT NO: ☐☐☐

Twelve Month Follow-up Questionnaire

	Please answer by only ONE box to the right.		
1.	How long after the procedure did you feel that you had completely recovered?	I have not recovered yet	
		Less than 2 weeks	
		2 to 4 weeks	
		4 to 8 weeks	
		2 to 3 months	
		3 to 6 months	
		6 to 12 months	
2.	When were you able to return to your normal everyday activities (housework, work, etc.)	Less than 2 weeks	
		2 to 4 weeks	
		4 to 8 weeks	
		2 to 3 months	
		3 to 6 months	
		6 to 12 months	
3.	Have your periods	Stopped	
		Continued but lighter	
		Continued as before	
		Continued but heavier	
4.	Do you have pain with your period?	No	
		Less than before	
		Same as before	
		Worse than before	
5.	Do your periods stop you from carrying out your work outside the home?	No, not at all	
		No, but work suffers	
		Yes, but only one day	
		Yes, more than one day	

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Pt. Initials & Date

MICROSULIS

Twelve Month Follow-up Questionnaire (continued)

PATIENT INITIALS: ☐☐☐

PATIENT NO: ☐☐☐☐

6.	Do your periods interfere with household and/or leisure activities?	No, not at all Mildly affected Moderately affected Severely affected Totally prevents it	
7.	Since the procedure are you experiencing any new or different pelvic pain?	No Sometimes Regularly Continually	
8.	Did you find the operation acceptable?	Yes No	
9.	Please indicate how you would rate your overall satisfaction with your treatment	Very satisfied Satisfied Dissatisfied	
10.	Have you had any other treatment for heavy periods since your study treatment?	No Yes	

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Pt. Initials & Date

1.3 Information Sheet and Questionnaire Outpatient Trial

INFORMATION SHEET FOR WOMEN HAVING M.E.A. UNDER LOCAL ANAESTHETIC

STUDY TO ASSESS THE VALUE OF HORMONAL MEDICATION BEFORE M.E.A (MICROWAVE ENDOMETRIAL ABLATION) TREATMENT

You have been referred for microwave endometrial ablation (M.E.A.) to treat your period problems.Traditionally women having endometrial ablation operations have been prescribed hormone treatment, either tablets or an injection, to thin the endometrium,(womb lining) before surgery.

Some surgeons have not used hormone treatment but have operated just after the woman's period instead.

For technical reasons it may be less important to use the hormones before M.E.A. than before the original types of endometrial ablation called T.C.R.E. (transcervical resection of the endometrium) or laser ablation.

There could be definite advantages for patients if the hormone treatment could be avoided. However, before changing our advice for everyone, it is important that we know whether M.E.A is just as successful without hormones as it is when they are used.

To do this we need to do a study where some women receive hormones before M.E.A. and some women don't.

We can only offer this to women having their M.E.A. under local anaesthetic.

You are invited to take part in the study. If you took part you would be allocated either M.E.A after hormone treatment or M.E.A. after a period. The allocation would be made randomly, like "rolling a dice". There would be a 50:50 chance of receiving hormone treatment or of having treatment after a natural period.

Women having hormone treatment would be given an operation date for the end of their 5 weeks treatment. Women having M.E.A. after a period would be asked to phone in when they get a period to arrange the operation for a date within the next 10 days.

If you took part in the study you would be asked to fill in a questionnaire before your treatment and again at 2 weeks, 4 months and 1 year after treatment.

It is completely up to you whether you take part in the study and you could withdraw from the study at any time without giving a reason and without any effect on your future medical care.
If you did not want to take part in the study you would receive standard hormone preparation and have your operation planned for 5 weeks after starting this.
All information collected as part of the study is confidential.

Please contact me on the number below to confirm whether or not you would like to take part in the study
and to make arrangements for your M.E.A. operation. I will be happy to answer any questions you may have.

Dr Stuart Jack, Clinical Research Fellow in Gynaecology.
01224 681818 bleep 3195 between 9am and 5pm Monday-Friday / Voicemail after 5pm or weekends -01224 559340.

UNIT NO. _____

MICROWAVE ENDOMETRIAL ABLATION

CONFIDENTIAL

DR STUART JACK
WARD 43, ABERDEEN ROYAL INFIRMARY
ABERDEEN AB25 2ZN

Tel: 01224 681818 ext. 53429 OR Bleep 3195

PATIENT STUDY CONSENT FORM.

MICROWAVE ENDOMETRIAL ABLATION (M.E.A.)
STUDY TO COMPARE TREATMENT AFTER HORMONE PREPARATION OR AFTER A PERIOD
ABERDEEN ROYAL INFIRMARY, DEPARTMENT OF GYNAECOLOGY
DR COOPER, DR PARKIN, DR JACK

Patient Name _____

Hospital Number _____ **Study Number**

_____

I have read the patient information sheet on the above study and have had the opportunity to discuss the details and ask questions.

The doctor has explained to me the nature and purpose of the study and I fully understand what is proposed to be done.

I understand that this study is part of a research project designed to promote medical knowledge and has been approved by the Joint Ethical Committee. The study may be of no benefit to me personally.

I understand that I can withdraw from the study at any time if I wish and that this will not affect my continuing medical care.

The information obtained from the study is confidential but my General Practitioner may be informed that I have taken part in it.

I consent to taking part in the study by completing questionnaires and also consent to being allocated either hormone treatment or treatment after a period, at random for my microwave endometrial ablation M.E.A. treatment.

Signed _____ **Date** _____

I confirm that I have fully explained the nature and the purpose of the study to the patient named above.

Name _____

Signed _____ **Date** _____

IF YOU WOULD HAVE HAD A STRONG PREFERANCE TO HAVING YOUR TREATMENT WITH OR WITHOUT DRUGS PLEASE STATE WHICH YOU WOULD HAVE PREFERED AND WHY.

The questionnaires are completely confidential.

When completing a questionnaire, please take your time and read the instructions carefully.

If you cannot answer a particular question leave it out and we will go through it with you later.

Please could you complete the following information to ensure we have up to date details in case we need to contact you.

NAME _____

ADDRESS _____

_____

_____

TELEPHONE _____ **WORK**

_____ **HOME**

G.P. NAME _____

ADDRESS _____

_____

_____

Patient Questionnaire for Before the Treatment

Thank you for completing this questionnaire while you are waiting for your M.E.A.
Please take your time and ask for help if any questions are not clear.
All the information is confidential and your answers will not affect your treatment in any way.

1/ How long have you had trouble with your periods?

- less than 1 year ☐
- 1 to 3 years ☐
- more than 3 years ☐

2/ On average do your periods come every 21-35 days

- Yes ☐
- No ☐

3/ Would you describe your periods as

- light ☐
- moderate ☐
- heavy with clots ☐
- very heavy with flooding ☐

4/ On average, how many days does your period last?

- less than 7 days ☐
- more than 7 days ☐

5/ On average for how many days is the bleeding heavy?

- not heavy ☐
- 1 to 3 days ☐

4 to 6 days ☐

7 or more days ☐

6/ Are your periods usually painful?

Yes ☐

No ☐

7/ Do you often get period pain more than a day before the bleeding starts?

Yes ☐

No ☐

8/ Imagine an average period for you; for each day of a period please show how severe your bleeding and pain were by giving each day a score from 1 to 5. Only fill in for the usual number of days your period lasts.

(1 is mild bleeding/pain, 5 is the worst bleeding/pain you can think of)

Day of period	bleeding score	pain score
Day 1	☐	☐
Day 2	☐	☐
Day 3	☐	☐
Day 4	☐	☐
Day 5	☐	☐
Day 6	☐	☐
Day 7	☐	☐
Day 8	☐	☐
Day 9	☐	☐
Day 10	☐	☐

9/ Do you often have problems with abdominal pain or bloating unrelated to period time?

Yes ☐

No ☐

10 / At any time in the last three months have you needed to use more than one form of sanitary protection at a time?

no ☐

tampon and pad ☐

two pads ☐

tampon and two pads ☐

more than this, e.g. bath towel ☐

11a/ Have you had any of the following symptoms in the last 4 weeks.

Hot Flushes	☐	Headaches	☐
Feeling Sick	☐	Abdominal pain or bloating	☐
Skin Rashes or itching	☐	Backache	☐
Leg Cramps	☐	Weight Gain	☐
Feeling tearful or anxious or irritable	☐	Swelling of fingers or face	☐
Difficulty getting a good nights sleep	☐	Feeling very tired	☐
Heavier bleeding than usual	☐	Bleeding for longer than usual	☐

11b/ Have these symptoms affected your lifestyle ?

No, I have not had any of these symptoms ☐

Yes, I've not been my usual self but I've carried on ☐

Yes, I have had to change planned work, household or social activities ☐

12/ Do you do paid work outside the home?

Yes full time ☐

Yes part time ☐

No ☐

13/ Have you needed to arrange care for dependent children or elderly / disabled relatives

until you are back to normal after your treatment?

No ☐ Yes ☐

14/ The following questions are about how you feel in yourself at the moment. Tick the box which comes closest to how you have been feeling in the past week. Don't take too long over your replies: your immediate reaction to each item will probably be most accurate.

I feel tense or wound-up:

- **most of the time** ☐
- **a lot of the time** ☐
- **occasionally** ☐
- **not at all** ☐

I feel as if I am slowed down:

- nearly all the time ☐
- very often ☐
- sometimes ☐
- not at all ☐

I still enjoy the things I used to enjoy:

- definitely as much ☐
- not quite so much ☐
- only a little ☐
- hardly at all ☐

I get a sort of frightened feeling like "butterflies" in my stomach:

- **not at all** ☐
- **occasionally** ☐
- **quite often** ☐
- **very often** ☐

I get a sort of frightened feeling as if something awful is about to happen:

- **very definitely and quite badly** ☐
- **yes, but not too badly** ☐
- **a little but it doesn't worry me** ☐
- **not at all** ☐

I have lost interest in my appearance:

- definitely ☐
- I don't take as much care as I should ☐
- I may not take quite as much care ☐
- I take as much care as ever ☐

I can laugh and see the funny side of things:

- as much as I always could ☐
- not quite so much now ☐
- definitely not so much now ☐
- not at all ☐

I feel restless as if I have to be on the move:

- **very much indeed** ☐
- **quite a lot** ☐
- **not very much** ☐
- **not at all** ☐

Worrying thoughts go through my mind:

- **a great deal of the time** ☐
- **a lot of the time** ☐
- **time to time but not too often** ☐
- **only occasionally** ☐

I look forward with enjoyment to things:

- as much as I ever did ☐
- rather less than I used to ☐
- definitely less than I used too ☐
- hardly at all ☐

I feel cheerful:

- not at all ☐
- not often ☐
- sometimes ☐
- most of the time ☐

I get sudden feelings of panic:

- **very often indeed** ☐
- **quite often** ☐
- **not very often** ☐
- **not at all** ☐

I can sit at ease and feel relaxed:

- **definitely** ☐
- **usually** ☐
- **not often** ☐
- **not at all** ☐

I can enjoy a good book or radio or T.V. programme:

- often ☐
- sometimes ☐
- not often ☐
- very seldom ☐

15/ In general, would you say your health is ?

excellent	☐
very good	☐
good	☐
fair	☐
poor	☐

16/ Does your health limit you when you do the following activities?

	Yes	No
Moderate activities such as moving a table, hoovering, bowling or golf	☐	☐
Climbing several flights of stairs	☐	☐

17/ In the past 4 weeks have you had any of the following problems with work or other daily activities as a result of your physical health?

	Yes	No
Accomplished less than you would have liked	☐	☐

Were limited in the kind of work or activities you did ☐ ☐

18/ In the past 4 weeks have you had any of the following problems with work or other daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	Yes	No
Accomplished less than you would have liked	☐	☐
Did not do work or other activities as carefully as usual	☐	☐

19/ In the past 4 weeks how much has pain interfered with your normal activities?

- Not at all ☐
- A little bit ☐
- Moderately ☐
- Quite a bit ☐
- Extremely ☐

20/ In the last 4 weeks for how much time did you have a lot of energy?

- All of the time ☐
- Most of the time ☐
- A good bit of the time ☐
- Some of the time ☐

A little of the time ☐

None of the time ☐

21/ In the last 4 weeks for how much time did you feel calm and peaceful?

All of the time ☐

Most of the time ☐

A good bit of the time ☐

Some of the time ☐

A little of the time ☐

None of the time ☐

22/ In the last 4 weeks for how much time did you feel downhearted and low?

All of the time ☐

Most of the time ☐

A good bit of the time ☐

Some of the time ☐

A little of the time ☐

None of the time ☐

23/ In the last 4 weeks how much of the time have your physical health or emotional problems

interfered with your social activities (like visiting friends or relatives)

All of the time ☐

Most of the time ☐

A good bit of the time ☐

Some of the time ☐

A little of the time ☐

None of the time ☐

Thank you for filling in this questionnaire

Patient Questionnaire for After the Treatment

Please fill in a short while before you go home

We would like to find out how you feel about the treatment you have just had. It would be helpful if you could complete the following questions for us. Please be honest and answer as best you can. If you are having any difficulties please ask for assistance.

1/ The 20 groups of words below can be used to describe pain. Some of the words below may describe any pain you may have had during and after your treatment. Please read all the words. Then circle ONE word in each group, the one that best describes the pain. If no words in a group are like your pain leave that group out.

1	2	3	4
Flickering	Jumping	Pricking	Sharp
Quivering	Flashing	Boring	Cutting
Pulsing	Shooting	Drilling	Lacerating
Throbbing		Stabbing	
Beating		Lancing	
Pounding			

5	6	7	8
Pinching	Tugging	Hot	Tingling
Pressing	Pulling	Burning	Itchy
Gnawing	Wrenching	Scalding	Smarting
Cramping		Searing	Stinging
Crushing			

9	10	11	12

Dull	Tender	Tiring	Sickening
Sore	Taut	Exhausting	Suffocating
Hurting	Rasping		
Aching	Splitting		
Heavy			

13	14	15	16
Fearful	Punishing	Wretched	Annoying
Frightful	Gruelling	Blinding	Troublesome
Terrifying	Cruel		Miserable
	Vicious		Intense
	Killing		Unbearable

17	18	19	20
Spreading	Tight	Cool	Nagging
Radiating	Numb	Cold	Nauseating
Penetrating	Drawing	Freezing	Agonising
Piercing	Squeezing		Dreadful
	Tearing		Torturing

2/ People agree that the following six words represent pain / discomfort of increasing intensity:-

1	2	3	4	5	6
none	**mild**	**discomforting**	**distressing**	**horrible**	**excruciating**

Answer each question below, **writing the number** of the most appropriate word in the space beside the question.

a/ which number best describes the discomfort of the procedure you have just had?

b/ which number describes the discomfort of a cervical smear test? _____

c/ which number describes the discomfort of an internal (vaginal) examination?

d/ which number describes the worst toothache you ever had? _____

e/ which number describes the worst headache you ever had? _____

f/ which number describes the worst stomach ache you ever had? _____

3/ Please circle the number in the following list which you feel is closest to how acceptable your treatment was for you.

1	2	3	4	5	6
totally acceptable	**generally acceptable**	**fairly acceptable**	**fairly unacceptable**	**generally unacceptable**	**totally unacceptable**

4/ Would you be prepared to have a procedure in the same way in the future? Yes☐

No☐

If no, please state reason why below, e.g. discomfort, embarrassing, time-consuming etc.

5/ From your experience so far, would you recommend this treatment to a friend with period problems?

Yes ☐

No ☐

6/ Have you felt sick after the procedure?

No ☐

Yes ☐

Yes, and I have actually vomited ☐

7/ From your experience so far would you arrange to come in for your treatment in the same way if you were coming in again?

Yes ☐

No ☐

8/ The line below represents the range from totally unacceptable to totally acceptable.

Please put a cross on the line below at the position between the two extremes which you feel shows how acceptable your experience in theatre was today.

Totally **Totally**

ACCEPTABLE _____ **UNACCEPTABLE**

9/ How soon after the treatment did you feel ready to go home? (Please record the earliest time when you felt well enough to leave hospital rather than when you were actually collected)

less than 1 hour ☐
between 1-2 hours ☐
between 2-4 hours ☐
between 4-8 hours ☐
longer than 8 hours ☐

10/ If you **chose** whether to have hormones and arrange your operation in advance or to call when you got your period please write down any reasons below.

11/ Please note down any comments you have about your experiences today and the information you were given before coming to hospital.

Thank you very much for filling in this questionnaire. All the information is entirely confidential and is not filed in your hospital notes.

I will be sending you another questionnaire in 2 weeks time to see how you are getting on.

You will receive an information sheet with advice about recovery after M.E.A. before you leave today.

Operative Questionnaire

UNIT NO:☐☐☐☐☐☐☐☐

Operation date _____

L.M.P. _____

Age _____

Weight _____ Height _____ **B.M.I.** _____

Parity No. of vaginal deliveries _____

No. of Caesareans _____

Previous cervical surgery (L.L.E.T.Z. / laser cone) Yes ☐

No ☐

Endometrial preparation none ☐

Danazol ☐

Zoladex ☐

Zoladex x 2 ☐

Endometrial thickness _____mm

MEA probe size 6mm probe ☐ 8mm probe ☐

Maximum force cervical dilation _____newtons

Cavity length _____cm

Hysteroscopy

normal	☐
polyp	☐
fibroid <2cm	☐
multiple fibroid	☐

Active Microwave time taken _____ seconds

Total procedure time _____ minutes
(From start iv site to leave room)

Needed IV midazolam?

no		☐
yes pre la		☐
yes for dilation		☐
hegar	_____	size
yes for MEA		☐

Total dose midazolam _____ mg

Needed opiate intra op? no ☐
yes ☐

MEA completed?

yes	☐
no, failed instrumentation	☐
no, uterine perforation blunt	☐
no, uterine perforation with active probe	☐
no need tcre	☐
no pain	☐
no anxiety	☐

Surgeon

Dr Cooper	☐
Dr Jack	☐

Pain relief post op

none	☐
oral	☐
im opiate	☐

Anti emetic postop

no	☐
yes	☐

When was patient **fit to leave** hospital? (i.e. drinking & comfortable)

<2 hours post op	☐
by 4 hours post op	☐
by 6 hours post op	☐
by 8 hours post op	☐
following day	☐

If **overnight stay** give reason:

pain	☐
nausea/vomit	☐

If seen on ward within 6 weeks of operation please write diagnosis and outcome.

UNIT NO. _____

MICROWAVE ENDOMETRIAL ABLATION

CONFIDENTIAL

PATIENT QUESTIONNAIRE
FOR TWO WEEKS AFTER M.E.A.

DR Stuart Jack
DUGALD BAIRD CENTRE, ABERDEEN ROYAL INFIRMARY
ABERDEEN AB25 2ZN

Tel: 01224 681818 ext. 53429 OR Bleep 3195

It is now 2 weeks after your M.E.A. operation. I hope you are recovering well.

I would be grateful if you could complete the following questionnaire about how you are getting on.

Please contact me if you have any questions about your operation or recovery.

1/ Did you have discomfort after you went home?

- Not really ☐
- Yes, like my usual period pain ☐
- Yes, worse than period pain but relieved by painkillers ☐
- Yes very severe pain but relieved by painkillers ☐
- Yes very severe pain which kept me awake despite painkillers ☐

2/ Did you need any painkillers after you went home?

- No ☐
- Yes, day of operation only ☐
- Yes, for 1 day after ☐
- Yes, for 2-3 days after ☐
- Yes, for more than 3 days ☐

3/ Did you have any feelings of sickness after you went home?

- No ☐
- Yes, I felt sick the day I went home ☐
- Yes, I felt sick and actually vomited the day I went home ☐
- Yes, I felt sick for more than 1 day ☐
- Yes, I felt sick and actually vomited for more than 1 day ☐

4/ Did you see your G.P. in the first 2 weeks after the operation?

- No ☐
- Yes ☐

5/ If yes what was the reason? (tick all that apply)

- pain ☐
- fever ☐
- vaginal bleeding / discharge ☐
- other, unrelated to the operation ☐

6/ If you saw your G.P. within 2 weeks of surgery what was the outcome?
(tick all that apply)

painkiller prescription	☐
antibiotic prescription	☐
seen at hospital as emergency	☐

7/ Please circle the number in the following list which you feel is closest to how acceptable the procedure was to you.

1	**2**	**3**	**4**	**5**	**6**
totally acceptable	generally acceptable	fairly acceptable	fairly unacceptable	generally unacceptable	totally unacceptable

8/ It is too soon to see any effects of the operation on your periods, but from your experience so far, would you recommend this procedure to a friend with period problems?

Yes ☐
No ☐

9/ If you needed the operation again would you want to arrange it in the same way?

Yes, I would prefer to have the hormones and know the date 5 weeks ahead ☐

Yes, I would prefer to wait for my period and phone in for a date that week ☐

No, I would prefer to have hormones and know the date 5 weeks ahead ☐

No, I would prefer to wait for a period and phone in for a date that week ☐

10/ What would you have been doing if you had not been in hospital that day?
(tick all that apply)

paid work ☐
housework ☐
care of child/ relative/ friend ☐
education ☐

11/ How physically demanding is the type of work you do?

sedentary work e.g. office ☐
involves prolonged standing ☐
light physical work e.g. driving ☐
heavy physical work ☐
care of pre-school children /
physically dependent adult ☐

12/ How many days was it before you felt well enough to go back to your normal activities (work/housework/childcare)?

day after operation ☐

2-3 days ☐

4-7 days ☐

8-14 days ☐

more than 2 weeks ☐

13/ Did anyone need to take time off from their normal activity to look after you or your children/relatives while you were in hospital or recovering?

No ☐

Yes ☐

If yes, please write down how many days:

_____ days

Thank you for completing this questionnaire. All the information is confidential. Please return it in the enclosed prepaid envelope.

STUDY NO: _____

MICROWAVE ENDOMETRIAL ABLATION

CONFIDENTIAL

PATIENT QUESTIONNAIRE

FOR SIX MONTHS AFTER M.E.A.

Dr STUART JACK

DUGALD BAIRD CENTRE, ABERDEEN ROYAL INFIRMARY

ABERDEEN AB25 2ZN

Tel 01224 681818 bleep 3195

PART A

It is now 6 months since your MEA.

You may be noticing some effects of the treatment already.

I would be very grateful if you could complete the following questionnaire and return it in the enclosed prepaid envelope.

1/ How soon after treatment did you return to normal everyday activities?

Within 2 weeks ☐

2-4 weeks ☐

more than 4 weeks ☐

2/ How long did the vaginal bleeding / discharge last after the treatment?

(enough to need a pad)

Less than 3 weeks ☐

3-5 weeks ☐

more than 5 weeks ☐

3/ After the treatment did you have any problems with hot flushes or headaches or feeling unusually tired or easily upset?

Yes ☐

No ☐

4/ If you had these problems how soon did they settle down?

Within 2 weeks ☐

In 2-4 weeks ☐

More than 4weeks ☐

5/ Since the postoperative bleeding/discharge settled after the MEA your periods may have changed from the way they were before the treatment. Have they:

stopped altogether ☐

become lighter ☐

stayed the same ☐

become heavier ☐

6/ If you are still having periods how long do they last?

Less than 3 days ☐

3-7 days ☐

more than 7 days ☐

7/ If you are still having periods how long is the bleeding heavy?

- Not heavy ☐
- Less than 3 days ☐
- 3-7 days ☐
- more than 7 days ☐

8/ Are you having any abdominal pain?

- No ☐
- Yes with periods ☐
- Yes at period time even though there is little/no bleeding ☐
- Yes, most weeks of the month ☐

9/ Imagine an average period for you since the treatment; for each day of a period please show how severe your bleeding and pain were by giving each day a score from 1 to 5. Only fill in for the number of days your period lasts.
(1 is mild bleeding/pain, 5 is the worst bleeding/pain you can think of)

Day of period	bleeding score	pain score
Day 1	☐	☐
Day 2	☐	☐
Day 3	☐	☐
Day 4	☐	☐
Day 5	☐	☐
Day 6	☐	☐
Day 7	☐	☐

Day 8	☐	☐
Day 9	☐	☐
Day 10	☐	☐

10/ Since the bleeding stopped after the MEA treatment have you needed to use more than 1 type of sanitary protection at a time?

No	☐
Yes 2pads	☐
Pad and tampon	☐
Other e.g bath towel	☐

11/ From your experience so far would you recommend this treatment to a friend with period problems?

Yes	☐
No	☐

12/ Please circle the number in the following list which you feel is closest to how satisfied you are with the MEA treatment.

1	2	3	4	5	6
totally satisfied	generally satisfied	fairly satisfied	fairly unsatisfied	generally unsatisfied	totally unsatisfied

13/ In general, would you say your health is ?

excellent	☐
very good	☐
good	☐
fair	☐
poor	☐

14/ Does your health limit you when you do the following activities?

	Yes	No
Moderate activities such as moving a table, hoovering, bowling or golf	☐	☐
Climbing several flights of stairs	☐	☐

15/ In the past 4 weeks have you had any of the following problems with work or other daily activities as a result of your physical health?

	Yes	No
Accomplished less than you would have liked	☐	☐
Were limited in the kind of work or activities you did	☐	☐

16/ In the past 4 weeks have you had any of the following problems with work or other daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	Yes	No
Accomplished less than you would have liked	☐	☐
Did not do work or other activities as carefully as usual	☐	☐

17/ In the past 4 weeks how much has pain interfered with your normal activities?

- Not at all ☐
- A little bit ☐
- Moderately ☐
- Quite a bit ☐
- Extremely ☐

18/ In the last 4 weeks for how much time did you have a lot of energy?

- All of the time ☐
- Most of the time ☐
- A good bit of the time ☐
- Some of the time ☐
- A little of the time ☐
- None of the time ☐

19/ In the last 4 weeks for how much time did you feel calm and peaceful?

- All of the time ☐
- Most of the time ☐
- A good bit of the time ☐
- Some of the time ☐
- A little of the time ☐
- None of the time ☐

20/ In the last 4 weeks for how much time did you feel downhearted and low?

All of the time ☐
Most of the time ☐
A good bit of the time ☐
Some of the time ☐
A little of the time ☐
None of the time ☐

21/ In the last 4 weeks how much of the time have your physical health or emotional problems interfered with your social activities (like visiting friends or relatives)

All of the time ☐
Most of the time ☐
A good bit of the time ☐
Some of the time ☐
A little of the time ☐
None of the time ☐

PART B

The purpose of the remaining questions are to find out:

1. Whether you have visited either your **General Practitioner (GP) or Aberdeen Royal Infirmary** in relation to your **menstrual problems** in the **last 5 months (i.e. since you last completed a costing questionnaire).**

2. Any **costs to you and your family** associated with these visits. These costs may include costs of travelling to the GP or hospital, time off work and costs of someone accompanying you to this appointment.

3. **Additional time** taken off **paid work and usual activities** due to menstrual problems in the **last 5 months**.

Q1a/ Over the **last 5 months** how many times have you visited your **GP for your menstrual problems?** Please write the number of times in the box below. (Put zero if you have not visited your GP over the last 5 months for your menstrual problems).

Number of visits | | |

If you answered 1 or more to the question above please continue with Question 1b. Otherwise, GO TO QUESTION 5a.

Q1b/ If you saw your GP in relation to your menstrual problems, what was the outcome? Please circle.

Painkiller prescription 1

Antibiotic prescription 2
Referral to Aberdeen Royal Infirmary 3
Tests (please specify) 4
Other (please specify) 5

Q2a/ When you visited the GP, how did you **normally** travel? Please circle one number which describes the **main** way you travelled.

Walked 1

Cycled 2
Public transport (eg bus, train or taxi) 3
Private car/motorbike 4
Other (please specify) 5

Q2b/ If you **normally** travelled by **public transport** (e.g. bus, train or taxi) for part or the whole journey, what was the cost of the (return) fare?

Cost of (return) fare (£) [ ][ ] – [ ][ ] Pence

Q2c/ If you **normally** travelled by **private car or motorbike** for part or the whole journey, about how many **miles** did you travel (return)?

Number of miles (return) [ ][ ][ ]

Q2d/ If you **normally** travelled by **private car or motorbike** for part, or all of the journey and had to pay **parking fees** how much did these amount to?

Cost of parking fees (£) [ ][ ] – [ ][ ] Pence

Q3a/ When you visited the **GP**, how long did it **normally** take you? Please include **travel time, waiting time and time taken to see the doctor** in your answer.

Number of hours [ ][ ] – [ ][ ] Minutes

Q3b/ What would you **normally** have **otherwise** been doing as your **main activity** if you had not had to attend the GP? Please circle one number that best describes this.

Housework 1
Childcare 2
Caring for a relative or friend 3
Voluntary work 4
Leisure activities 5
Attending school or university 6

On sick leave 7

Paid work (employed/self employed) 8

Other (please specify) 9

Q4a/ Did anyone **normally** accompany you to the GP? Please circle.

Yes 1

No ..... 2 GO TO QUESTION 5a

Q4b/ Who was the **main person** who **normally** accompanied you to the GP? Please circle.

Partner/spouse 1

Child/children under 16 years 2

Other relative 3

Paid caregiver 4

Other (please specify) 5

Q4c/ What would your main companion **normally** otherwise have been doing as their **main activity** if they had not accompanied you to the GP? Please circle.

Housework 1
Childcare 2
Caring for a relative or friend 3
Voluntary work 4
Leisure activities 5
Attending school or university 6
On sick leave 7

Paid work (employed/self employed) 8

Other (please specify) 9

Q5a/ Over the **last 5 months** how many times have you visited **Aberdeen Royal Infirmary for your menstrual problems?** Please write the number of times in the box below. (Put zero if you have not visited the hospital over the last 5 months for your menstrual problems).

Number of visits | | |

If you answered 1 or more to the question above please continue with Question 5b. Otherwise, GO TO QUESTION 9.

Q5b/ Please indicate the nature of your visit/s at Aberdeen Royal Infirmary. Please circle.

An appointment at the Menstrual Clinic **1**

An appointment with Dr Stuart Jack on Ward 42/43 2

Admitted for a menstrual related operation (please specify) 3

Other (please specify) 4

Q6a/ When you visited **Aberdeen Royal Infirmary**, how long did you **normally** spend at the hospital? Please include waiting time and time taken to see the doctor in your answer.

Number of hours ☐☐ – ☐☐ Minutes

Q6b/ What would you have **otherwise** been **normally** doing as your **main activity** if you had not had to attend the hospital? Please circle one number that best describes this.

Housework 1

Childcare 2

Caring for a relative or friend 3

Voluntary work 4

Leisure activities 5

Attending school or university 6

On sick leave 7

Paid work (employed/self employed) 8

Other (please specify) 9

Q7a/ Did anyone **normally** accompany you to the hospital? Please circle.

Yes 1

No ..... 2 GO TO QUESTION 8a

Q7b/ Who was the **main person** who **normally** accompanied you to the hospital? Please circle.

Partner/spouse 1

Child/children under 16 years 2

Other relative 3

Paid caregiver 4

Other (please specify) 5

Q7c/ What would your main companion otherwise have been **normally** doing as their **main activity** if they had not accompanied you to the hospital? Please circle.

Housework 1
Childcare 2
Caring for a relative or friend 3
Voluntary work 4
Leisure activities 5
Attending school or university 6
On sick leave 7

Paid work (employed/self employed) 8

Other (please specify 9

The following questions ask whether you required any **additional assistance** to look after your **dependants** for example, children, elderly relatives etc. when you visited the **hospital or during your recovery in the last 5 months**. We are only interested in assistance, which was **in addition to your usual care arrangements.**

Q8a/ Did you get someone to look after your dependants? Please circle.

Yes 1
No 2
Not applicable .....8 } **GO TO QUESTION**

Q8b/ How many hours in total did they spend looking after your dependants while you were in hospital and when you were recovering in the last 5 months?

Number of hours ☐☐ – ☐☐ Minutes

Q8c/ Please think about the **main** caregiver, that is the person who you consider most needed to be with your dependants. Did you pay that person to look after your dependants? Please circle.

Yes .....1 GO TO QUESTION 9
No 2

Q8d/ If they were **not paid**, what would that person have been doing as their **main** activity if they had not been looking after your dependants? Please circle.

Housework 1
Childcare 2
Caring for a relative or friend 3
Voluntary work 4
Leisure activities 5
Attending school or university 6

On sick leave 7

Paid work (employed/self employed) 8

Other (please specify) 9

Q9/ In the last 5 months, how many days or weeks have you taken off **paid work** as a result of your **menstrual problems (excluding the time taken to visit the GP and Aberdeen Royal Infirmary)**?

Number of weeks ☐☐ – ☐☐ Days

Q10/ We are interested in whether your **normal activities** have been affected by your menstrual problems in the last 5 months. Could you please indicate whether any of the normal activities have been affected in the **last 5 months** and if so, how they have been affected?

Normal activities	**Please circle**	***If YES, please explain***
Paid work	Yes / No	
Housework	Yes / No	
Childcare	Yes / No	
Caring for a relative/ friend	Yes / No	
Voluntary work	Yes / No	
Leisure activities	Yes / No	
Attending school or university	Yes / No	

Thank you for filling in this questionnaire

STUDY NO:_____

MICROWAVE ENDOMETRIAL ABLATION

CONFIDENTIAL

PATIENT QUESTIONNAIRE

FOR 1 YEAR AFTER M.E.A.

Dr Stuart Jack

DUGALD BAIRD CENTRE, ABERDEEN ROYAL INFIRMARY

ABERDEEN AB25 2ZN

Tel 01224 681818 bleep 3195 ext 53429

It is now a year since your MEA treatment and we would like to hear how you are getting on, even if you have been back to the gynaecology department for an appointment or treatment meanwhile.

I would be very grateful if you could complete the following questionnaire and return it in the enclosed prepaid envelope.

Please get in contact if there is anything related to your treatment that you would like to discuss further.

1/ Compared with the way things were before the MEA treatment have your periods:

- stopped altogether ☐
- become lighter ☐
- stayed the same ☐
- become heavier ☐

2/ If you are still having periods how long do they last?

- Less than 3 days ☐
- 3-7 days ☐
- more than 7 days ☐

3/ If you are still having periods how long is the bleeding heavy?

- Not heavy ☐
- Less than 3 days ☐
- 3-7 days ☐
- more than 7 days ☐

4/ Are you having any abdominal pain?

No	☐
Yes with periods	☐
Yes at period time even though there is little/no bleeding	☐
Yes, most weeks of the month	☐

5/ Compared with the way things were before the MEA treatment, is the pain:

worse, it only started since MEA	☐
worse than before	☐
unchanged	☐
improved but still a problem	☐
improved, not a problem now	☐
I've had no problems with pain before or since the MEA	☐

6/ Since the bleeding stopped after the MEA treatment have you needed to use more than one type of sanitary protection at a time?

No	☐
Yes 2 pads	☐
Pad and tampon	☐
Other e.g. bath towel	☐

7/ Imagine an average period for you in the last 4 months. For each day of a period please show how severe your bleeding and pain were by giving each day a score from 1 to 5. Only fill in for the number of days your period lasts.

(1 is mild bleeding/pain, 5 is the worst bleeding/pain you can think of)

Day of period	bleeding score	pain score
Day 1	☐	☐
Day 2	☐	☐
Day 3	☐	☐
Day 4	☐	☐
Day 5	☐	☐
Day 6	☐	☐
Day 7	☐	☐
Day 8	☐	☐
Day 9	☐	☐
Day 10	☐	☐

8/ From your experience so far would you recommend this treatment to a friend with period problems?

Yes ☐

No ☐

9/ Please circle the number in the following list which you feel is closest to how satisfied you are with the results of the MEA treatment.

1	**2**	**3**	**4**	**5**	**6**
totally satisfied	generally satisfied	fairly satisfied	fairly unsatisfied	generally unsatisfied	totally unsatisfied

10/ Have you been back to the gynaecology department since your treatment?

No	☐
Yes to do with my periods	☐
Yes for another reason	☐

11/ Have you had, or are you on the waiting list to have more gynaecological surgery?

No	☐
Yes	☐

12/ The following questions are about how you feel in yourself at the moment.
Tick the box which comes closest to how you have been feeling in the past week.
Don't take too long over your replies: your immediate reaction to each item will probably be most accurate.

I feel tense or wound-up:		I feel as if I am slowed down:	
most of the time	☐	nearly all the time	☐
a lot of the time	☐	very often	☐
occasionally	☐	sometimes	☐
not at all	☐	not at all	☐

I still enjoy the things I used to enjoy:		**I get a sort of frightened feeling like "butterflies" in my stomach:**	
definitely as much	☐	**not at all**	☐
not quite so much	☐	**occasionally**	☐
only a little	☐	**quite often**	☐
hardly at all	☐	**very often**	☐

I get a sort of frightened feeling as if something awful is about to happen:		I have lost interest in my appearance:	
very definitely and quite badly	☐	definitely	☐
yes, but not too badly	☐	I don't take as much care as I shoul	☐
a little but it doesn't worry me	☐	I may not take quite as much care	☐
not at all	☐	I take as much care as ever	☐

I can laugh and see the funny side of things:

- as much as I always could ☐
- not quite so much now ☐
- definitely not so much now ☐
- not at all ☐

I feel restless as if I have to be on the move:

- **very much indeed** ☐
- **quite a lot** ☐
- **not very much** ☐
- **not at all** ☐

Worrying thoughts go through my mind:

- **a great deal of the time** ☐
- **a lot of the time** ☐
- **time to time but not too often** ☐
- **only occasionally** ☐

I look forward with enjoyment to things:

- as much as I ever did ☐
- rather less than I used to ☐
- definitely less than I used too ☐
- hardly at all ☐

I feel cheerful:

- not at all ☐
- not often ☐
- sometimes ☐
- most of the time ☐

I get sudden feelings of panic:

- **very often indeed** ☐
- **quite often** ☐
- **not very often** ☐
- **not at all** ☐

I can sit at ease and feel relaxed:

- **definitely** ☐
- **usually** ☐
- **not often** ☐
- **not at all** ☐

I can enjoy a good book or radio or T.V. programme:

- often ☐
- sometimes ☐
- not often ☐
- very seldom ☐

13/ In general, would you say your health is?

excellent	☐
very good	☐
good	☐
fair	☐
poor	☐

14/ Does your health limit you when you do the following activities?

	Yes	No
Moderate activities such as moving a table, hoovering, bowling or golf	☐	☐
Climbing several flights of stairs	☐	☐

15/ In the past 4 weeks have you had any of the following problems with work or other daily activities as a result of your physical health?

	Yes	No
Accomplished less than you would have liked	☐	☐
Were limited in the kind of work or activities you did	☐	☐

16/ In the past 4 weeks have you had any of the following problems with work or other daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	Yes	No
Accomplished less than you would have liked	☐	☐
Did not do work or other activities as carefully as usual	☐	☐

17/ In the past 4 weeks how much has pain interfered with your normal activities?

- Not at all ☐
- A little bit ☐
- Moderately ☐
- Quite a bit ☐
- Extremely ☐

18/ In the last 4 weeks for how much time did you have a lot of energy?

- All of the time ☐
- Most of the time ☐
- A good bit of the time ☐
- Some of the time ☐
- A little of the time ☐
- None of the time ☐

19/ In the last 4 weeks for how much time did you feel calm and peaceful?

- All of the time ☐
- Most of the time ☐
- A good bit of the time ☐
- Some of the time ☐
- A little of the time ☐
- None of the time ☐

20/ In the last 4 weeks for how much time did you feel downhearted and low?

- All of the time ☐
- Most of the time ☐
- A good bit of the time ☐
- Some of the time ☐
- A little of the time ☐
- None of the time ☐

21/ In the last 4 weeks how much of the time have your physical health or emotional problems interfered with your social activities (like visiting friends or relatives)

All of the time	☐
Most of the time	☐
A good bit of the time	☐
Some of the time	☐
A little of the time	☐
None of the time	☐

PART B

The purpose of the remaining questions are to find out:

4. Whether you have visited either your **General Practitioner (GP) or Aberdeen Royal Infirmary** in relation to your **menstrual problems** in the **last 6 months (i.e. since you last completed a costing questionnaire).**

5. Any **costs to you and your family** associated with these visits. These costs may include costs of travelling to the GP or hospital, time off work and costs of someone accompanying you to this appointment.

6. **Additional time** taken off **paid work and usual activities** due to menstrual problems in the **last 6 months**.

Q1a. Over the **last 6 months** how many times have you visited your **GP for your menstrual problems?** Please write the number of times in the box below. (Put zero if you have not visited your GP over the last 6 months for your menstrual problems).

Number of visits ☐☐

If you answered 1 or more to the question above please continue with Question 1b. Otherwise, GO TO QUESTION 5a.

Q1b. If you saw your GP in relation to your menstrual problems, what was the outcome? Please circle.

Pain killer prescription 1

Antibiotic prescription 2

Referral to Aberdeen Royal Infirmary 3

Tests (please specify) **4**

Other (please specify)..... 5

Q2a. When you visited the GP, how did you **normally** travel? Please circle one number which describes the **main** way you travelled.

Walked 1

Cycled.....2

Public transport (eg bus, train or taxi) 3

Private car/motorbike.....4

Other (please specify)..... 5

}GO TO QUESTION 3a

Q2b. If you **normally** travelled by **public transport** (e.g. bus, train or taxi) for part or the whole journey, what was the cost of the (return) fare?

Cost of (return) fare (£) ☐☐ – ☐☐ Pence

Q2c. If you **normally** travelled by **private car or motorbike** for part or the whole journey, about how many **miles** did you travel (return)?

Number of miles (return) ☐☐☐

Q2d. If you **normally** travelled by **private car or motorbike** for part or all of the journey and had to pay **parking fees** how much did these amount to?

Cost of parking fees (£) ☐☐ – ☐☐ Pence

Q3a. When you visited the **GP**, how long did it **normally** take you? Please include **travel time, waiting time and time taken to see the doctor** in your answer.

Number of hours ☐☐ – ☐☐ Minutes

Q3b. What would you **normally** have **otherwise** been doing as your **main activity** if you had not had to attend the GP? Please circle one number that best describes this.

Housework 1
Childcare 2
Caring for a relative or friend 3
Voluntary work 4
Leisure activities 5
Attending school or university 6

On sick leave 7

Paid work (employed/self employed) 8
Other (please specify)..... 9

Q4a. Did anyone **normally** accompany you to the GP? Please circle.

Yes 1

No ..... 2 GO TO QUESTION 5a

Q4b. Who was the **main person** who **normally** accompanied you to the GP? Please circle.

Partner/spouse 1

Child/children under 16 years 2

Other relative 3

Paid caregiver 4

Other (please specify) 5

Q4c. What would your main companion **normally** otherwise have been doing as their **main activity** if they had not accompanied you to the GP? Please circle.

Housework 1
Childcare 2
Caring for a relative or friend 3
Voluntary work 4
Leisure activities 5
Attending school or university 6
On sick leave 7

Paid work (employed/self employed) 8

Other (please specify) 9

Q5a. Over the **last 6 months,** since your last MEA questionnaire, how many times have you visited **Aberdeen Royal Infirmary for your menstrual problems?** Please write the number of times in the box below. (Put zero if you have not visited the hospital over the last 6 months for your menstrual problems).

Number of visits ☐☐

If you answered 1 or more to the question above please continue with Question 5b. Otherwise, GO TO QUESTION 9.

Q5b. Please indicate the nature of your visit/s at Aberdeen Royal Infirmary. Please circle.

An appointment at the Menstrual Clinic.....1

An appointment with Dr Stuart Jack on Ward 42/43.....2

Admitted for a menstrual related operation (please specify).....3

Other (please specify).....4

Q6a. When you visited **Aberdeen Royal Infirmary**, how long did you **normally** spend at the hospital? Please include waiting time and time taken to see the doctor in your answer.

Number of hours ☐☐ - ☐☐ Minutes

Q6b. What would you have **otherwise** been **normally** doing as your **main activity** if you had not had to attend the hospital? Please circle one number that best describes this.

Housework 1

Childcare 2

Caring for a relative or friend..... 3

Voluntary work 4

Leisure activities 5

Attending school or university 6

On sick leave 7

Paid work (employed/self employed)..... 8

Other (please specify)..... 9

Q7a. Did anyone **normally** accompany you to the hospital? Please circle.

Yes 1

No..... 2 GO TO QUESTION 8a

Q7b. Who was the **main person** who **normally** accompanied you to the hospital? Please circle.

Partner/spouse 1

Child/children under 16 years..... 2

Other relative..... 3

Paid caregiver..... 4

Other (please specify)..... 5

Q7c. What would your main companion otherwise have been **normally** doing as their **main activity** if they had not accompanied you to the hospital? Please circle.

Housework 1

Childcare 2

Caring for a relative or friend..... 3

Voluntary work 4

Leisure activities 5

Attending school or university 6

On sick leave 7

Paid work (employed/self employed)..... 8

Other (please specify)..... 9

The following questions ask whether you required any **additional assistance** to look after your **dependents** for example, children, elderly relatives etc when you visited the **hospital and/or during your recovery in the last 6 months**. We are only interested in assistance which was **in addition to your usual care arrangements.**

Q8a. Did you get someone to look after your dependents? Please circle.

Yes 1
No 2
Not applicable 8

} **GO TO QUESTION 9**

Q8b. How many hours in total did they spend looking after your dependents while you were in hospital and/or when you were recovering in the last 6 months?

Number of hours ☐☐ – ☐☐ Minutes

Q8c. Please think about the **main** caregiver, that is the person who you consider most needed to be with your dependents. Did you pay that person to look after your dependents? Please circle.

Yes..... 1
No..... 2 GO TO QUESTION9

.**Q8d.** If they were **not paid**, what would that person have been doing as their **main** activity if they had not been looking after your dependents? Please circle.

Housework 1
Childcare 2
Caring for a relative or friend 3
Voluntary work 4
Leisure activities 5
Attending school or university 6
On sick leave 7
Paid work (employed/self employed) 8
Other (please specify) 9

Q9. In the last 6 months, how many days or weeks have you taken off **paid work** as a result of your **menstrual problems (excluding the time taken to visit the GP and Aberdeen Royal Infirmary)**?

Number of weeks ☐☐ – ☐☐ Days

Q10. We are interested in whether your **normal activities** have been affected by your menstrual problems in the last 6 months. Could you please indicate whether any of the normal activities have been affected in the **last 6 months** and if so, how they have been affected?

Normal activities	**Please circle**	***If YES, please explain***
Paid work	Yes / No	
Housework	Yes / No	
Childcare	Yes / No	
Caring for a relative/ friend	Yes / No	
Voluntary work	Yes / No	
Leisure activities	Yes / No	
Attending school or university	Yes / No	

Thank you for filling in this questionnaire

Your answers are essential to help us plan treatment for women having MEA in the future.

Please get in contact if you have any questions about your treatment or recovery.

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Publications Resulting From this Thesis (CD ROM in Rear Folder Pocket)

1. Cooper KG, Jack SA, Parkin DE, Grant AM. Five-year follow up of women randomised to medical management or transcervical resection of the endometrium for heavy menstrual loss: clinical and quality of life outcomes. BJOG 2001; 108(12):1222-1228.

2. Jack SA, Cooper KG, Seymour J, Graham W, Fitzmaurice A, Perez J. A randomised controlled trial of microwave endometrial ablation without endometrial preparation in the outpatient setting: patient acceptability, treatment outcome and costs. BJOG: An International Journal of Obstetrics and Gynaecology 2005; 112(8):1109-1116.

3. Cooper J M, Anderson TL, Fortin CA, Jack SA, Plentl MB. Microwave endometrial ablation vs. rollerball electro- ablation for menorrhagia: a multicenter randomised trial. The Journal of The American Association of Gynecologic Laparoscopists 2004; 11(3): 394- 403.

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